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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

PUBLIC WORKSHOP - HEMOSTATIC MEDICAL DEVICES FOR TRAUMA USE

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September 3, 2014
8:00 a.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Bldg. 31, Room 1503A (Section A of the Great Room)
Silver Spring, MD 20993

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SESSION III - ASSESSING SAFETY AND EFFECTIVENESS

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M E E T I N G

(8:02 a.m.)

DR. ASHAR: Good morning, and welcome to the FDA White Oak campus in Silver Spring, Maryland. My name is Binita Ashar. I am the Director of the Division of Surgical Devices at the Center for Devices and Radiological Health here at the U.S. Food and Drug Administration. I am also a general surgeon.

So whether you are joining us here in person or remotely, we are delighted to have you today. At last count, we had approximately 100 people that had registered to attend in person and over 100 also registered to attend remotely. And by remotely, that includes both attendees that are national and international. So the FDA workshop planning team consisting of scientists, engineers, physicians, surgeons from across the Agency has assembled a background discussion paper that you could find either on the table outside or on the website advertising this conference.

With that discussion paper is an aggressive agenda that's going to be guiding us for the next day and a half. And the main goal is to see how we can all together work to maximize bench testing, animal testing, clinical testing, and postmarket testing to streamline the development and assessment of medical products intended to treat life-threatening hemorrhage whether it occurs in the civilian population or in the military population.

We here at the FDA are committed to the promotion of beneficial products that meet this urgent need to save lives and reduce suffering, and we hope that this conference will help make that happen.

So I just have a few housekeeping items. I wanted to emphasize that this is a scientific discussion that we are going to be having. This is intended to cause an open exchange of ideas and information. This is not an FDA advisory panel. This is not a panel where the participants and the speakers have been vetted for conflicts of interest. So unlike an advisory panel where we may be discussing issues that could be informing and developing policy, our focus today is on the science and not the development of regulatory policy.

So what I'd like for us to do is to focus on the science of how we, as academicians, as surgeons, as industry partners, regulators, and the military can all thoughtfully work together to expedite the benefit of these potential life-saving medical products.

So without further delay, I'd like to introduce our first keynote speaker for today, Colonel Todd Rasmussen. He is a busy vascular and trauma surgeon who is also the Director of the Department of Defense Combat Casualty Care Research Program.

Thank you very much.

DR. RASMUSSEN: Thank you, Binita. And thank you to the organizers of this outstanding venue. It's a real pleasure for me to be here

and to speak on this topic. And I would congratulate Binita and the organizers for having the courage to give me the microphone this early in the morning and asking me, post-call, to talk about hemostasis and control of bleeding.

So I'll only be here for about 3 or 4 hours, and I hope that's okay. Is that right, Binita? Do I have that long to talk?

I tried to find -- head for the door. I tried to find a photograph of a pig in mud because -- I couldn't find one, but for me to be able to talk, as a vascular trauma surgeon, about hemostasis and hemostatic devices is a real pleasure, so thank you again for this opportunity and for arranging such a great venue.

So, to start with, the word "hemorrhage," I thought it would be reasonable -- and I try to learn a little bit with each of these talks as to the origins of the word "hemorrhage." And the origin of the word "hemorrhage" is really shown here. It came from an English term *hemorrhagy* that really was derived from the Latin term *haemorrhagia*, and originally a Greek term, also *haimorrhagia*. And really that stemmed from the word *haima*, which was blood, and then the stem of the word, the Greek term*, rhēgnunai*, which is burst. And for any of you in the room who have seen a blood vessel burst, you can sort of understand how that term got linked in its origin to hemorrhage.

So, really, here are the origins of the word "hemorrhage," and I

thought that it would be fitting for us to look at that briefly as we talk about hemorrhage control devices and their role in the care of severely injured patients today. So it's a noun, "hemorrhage." It means, in the definition in the dictionary, escape of blood from a ruptured blood vessel, especially when profuse. And we'll discuss that over the next several hours today and tomorrow, about profuse bleeding and the effects that it causes on the physiology of the injured person.

As a vascular surgeon, I often thought of myself, really, as a glorified plumber. There was one time I was asked, as a vascular surgeon, how can you stand to do vasectomies all day long. And I thought no, no, no.

(Laughter.)

DR. RASMUSSEN: I'm not that. No, it's not -- I'm not a vasectomy doctor, I'm a vascular surgeon, which is more like a plumber. And this more, sort of -- this sort of plumbing.

And so when I was a vascular fellow in Rochester, you know, we were told to simplify and that blood vessels either get clogged up, they get aneurysmal and degenerate, or they'll burst. And so this is a photograph and then certainly a depiction of a burst pipe. And I think in some ways some of the devices we'll talk about over the next couple of days or next couple of hours and then tomorrow, you know, we can think about this as a pipe and maybe nothing quite so rudimentary as the clog here, but nonetheless a device to stop bleeding from -- or in this case, water hemorrhaging from the

broken pipe.

So what's new here this morning and why have we all invested time to get here, invested our efforts to put these talks and conversations, and for many of you, your time and effort to put together new thinking and new ways of thinking about hemorrhage control? What is new? Hemorrhage certainly is not new, and I didn't want to go into the history any more than the derivation of the word as to "hemorrhage," but certainly it's not new. War and conflict has been part of the earth for many millennia, so hemorrhage is not new.

So why are we here? And I would submit to you, acknowledging that I, wearing this uniform, am a bit biased, but I would submit to you that we're here this morning because of the momentum that has been gained from the sacrifices of really, at the risk of overstating it a bit, the sacrifices of a generation, the recent generation. So the current conflicts in Afghanistan and Iraq that was interspersed in this time, we've had a period of 156 consecutive months of combat operations of uniformed U.S. service personnel.

Now, to put that in perspective, we were in World War I for 21 months, okay? The death toll from World War I was hard to fathom and its impact on humanity is difficult to even characterize, but the U.S. was really only in that and had combat operations and the ability to learn from those combat operations for 21 months. World War II, again, the impact of that

war on humanity is difficult to even describe, but the U.S. combat operations and our ability to resurge and learn from trauma from that World War II was 45 months, so less than four years.

Korea. We were in Korea for 38 months. And even Vietnam, a very prolonged military conflict by all standards in this country, we were only in Vietnam for 100 months. So I would argue and submit that we are here today because of the momentum of 156 consecutive months of combat operations in Afghanistan. And really the burden of the wartime injury combined with the DoD's requirements-driven -- and I'm going to talk a little bit about what requirements-driven program research is or investment -- has resulted in this extraordinary occasion to improve trauma care.

And I put the burden of injury here, which is hopefully once-in-a-generation injury here, which is wounded U.S. service personnel as of last night, more than 52,000, and more than 6800 deaths. I think that that burden of injury, combined with the wherewithal to study -- so I think inquisitiveness and the wherewithal to study, this is -- I'm glad to see John Holcomb in the audience. This is a favorite quote from a discussion of a paper that he probably wrote in 2004 and 2005. It was published in 2006. But in the discussion it says, "If efforts are successful, the current war will be the first from which detailed analyses of epidemiology, severity of injury, trauma care, and outcomes can be used to guide research resources for combat casualty care."

And I think over the next number of hours we will see how those resources have come to bear on the topic of hemorrhage, hemorrhage control, and specifically, today and tomorrow, devices. But I think that was a prophetic sort of quote, and that was made, of course, or published eight years ago. It's probably really recognized nine or 10 years ago.

So where does bleeding come from? And this is a photograph of -- you know, I have this on my bedroom wall and my bathroom mirror so that I know, as a vascular surgeon, every day, you know, what encounters or what I may face in the operating room. Where does bleeding come from?

Well, it certainly comes from what are called axial vessels in the extremity, so when we use the term "axial vessels," that's sort of the main highway, that's the brachial artery or in this case maybe the axillary brachial radial and ulnar arteries. It also comes from soft tissues that -- in veins and superficial veins and arteries in the extremities. It comes from the head and cervical region. It comes from the torso, which is really defined as the thorax, abdomen, and pelvis. And then, importantly, this war has shown us the implications of junctional regions. And I will talk a little bit, review very briefly on a cursory level in this talk and then over the ensuing hours what junctional hemorrhage is and why that may be important.

In these categories it was important for us to define these because of the impact of hemorrhage. And I'm going to review some epidemiologic studies that have really shown how we have been able to

characterize the impact of hemorrhage, where it comes from. So we're going to -- if we're going to study it and then work to alleviate its impact, we need to know where the bleeding comes from. So these are the categories.

Now, if we look at the history and the history of World War II, this was a paper from Michael DeBakey published right after World War II. He stayed an extra year to catalog his experience with arterial injuries. Now, this was a sentinel paper, for sure, but it really focused on axial arterial injuries, so the arterial injuries of the brachial, femoral, popliteal, let's say, and he really didn't include too much the tibial or distal arteries, tibial arteries or radial or ulnar arteries. So it was a sentinel paper, but it didn't capture the entirety of vascular injury and hemorrhage, and the rate of vascular injury that he showed was about one out of all combat injured and it may actually have been deployed forces had a vascular injury.

So I share this with you as a historical context showing that at least initially, I think, that our understanding of hemorrhage was somewhat limited because of studies like this that looked only at vascular trauma, traditional vascular trauma, injury only to named axial vessels in the extremities mostly.

So this is another way to put it. This was a paper that Joe White did from the Institute of Surgical Research. Adam Stannard, a UK fellow or registrar, followed this up using the UK registrar, but we see that the contemporary rates of vascular trauma certainly are higher now than any

of the other wars, at least the recorded rates. It may very well be that we have better ways to record rates of vascular trauma now than in previous wars, and it may be that patients are surviving now because of hemostatic devices, to have their vascular injuries cataloged and documented in an electronic registry. But there were limitations to those studies. As I said, I think we were somewhat hamstrung, in a way, in understanding the extent of hemorrhage because the initial studies on vascular injury only focused on named axial vessels. They were studied by surgeons, and can we fix or do we have to ligate that vascular injury.

Those initial studies did not account for the full breadth or the whole burden of hemorrhage, which really arises from all sorts of vascular disruptions. So we've spent the last five or six years trying to propagate the term "vascular disruption" and recognizing that hemorrhage, yes, it comes from the femoral artery, but it could also come from a Grade 4 solid organ injury from the liver, kidney, or spleen. And that, in previous wars, it really wasn't cataloged as a vascular injury.

This is a paper that looked at the causes of death on the battlefield, which really, initially, this -- and one paper earlier to this. I couldn't find it quickly last night, but this was published in 2007. I believe there was one in 2006 that looked at the Armed Forces Medical Examiner's office and looked at the causes of death in this very short period of time, relatively short period of time, and the conclusions of this said that the

majority of deaths on the modern battlefield at that time were non-survivable. But it acknowledged right away that improved methods of intracavitary noncompressible hemostasis may increase survival. So, again, noncompressible, meaning not able to be compressed or controlled with a tourniquet. We'll talk a little bit about that in the coming slides.

So intracavitary, that presumably means intrathoracic, intra-abdominal, or in the pelvis; the cavity that is the torso, that I showed on the previous slide. This is really one of two studies that really first began to give us insight into the impact of intracavitary hemorrhage. This followed: this was another study in 2008 that was published, again looking at the causes of death on the battlefield. And if you look at the last sentence, it says, "Truncal hemorrhage is the leading cause of potentially survivable death. Arguably, success in medical improvements during this war serve to maintain the lowest case type on record." But here again it was mostly -- I point this out -- looking at truncal hemorrhage, the importance and impact of noncompressible hemorrhage, bleeding that is not able to be stemmed with direct pressure or a tourniquet.

Part of our effort to promulgate the broader definition of vascular injury was shown in this paper -- Johnny Morrison really led this -- where we looked at noncompressible torso hemorrhage and tried to give it a definition. For many years it was just noncompressible torso hemorrhage. What is that? Well, we tried, rudimentarily, in a rudimentary fashion, to give

it -- that means really bleeding from a thoracic cavity, including lung parenchyma. Solid organ injury, which is Grade 4-5: liver, kidney, spleen injury. And if one looks at the Grade 4-5, you see it's vascular disruption; it's vascular disruption of the hilum with hemorrhage. We looked at torso, certainly main axial vessel. Aorta, branch vessels off the aorta, vena cava and such is still noncompressible torso hemorrhage. And then pelvic fracture with ring disruption, okay. We didn't often think of that as a vascular injury, but really, it is because it disrupts the veins of the pelvis and there's bleeding in the pelvis and hemorrhage. So, in this paper that was really led by Johnny, we looked at and tried to put forth that pelvic fracture with ring disruption is also a form of noncompressible torso hemorrhage.

This was the MATTERs study that really looked at TXA. I show you the paper, the lead of this, because we really -- not to discuss tranexamic acid and medication in this conference, but if one looks here, we really purposely put the big V here in vascular disruption. So we led this article with vascular disruption with concomitant hemorrhage. So we tried to do this to try to get this out that vascular injury and hemorrhage isn't just a traditional SFA injury that was documented by Dr. DeBakey in World War II or Norm Rich in -- Frank Spencer in Korea, Norm Rich in Vietnam. Vascular disruption and hemorrhage can be anyplace in the body.

We applied the definition of noncompressible torso hemorrhage shown in the previous paper to the Department of Defense

Trauma Registry or DoDTR -- at the time, it was the Joint Theater Trauma Registry -- looking at and trying to see what the epidemiology of this definition was, at least in those who survived to have their injuries recorded. This did not include Armed Forces Medical Examiner's data. But the pattern, what we showed here was that the pattern of noncompressible torso injury occurs in more than 10% of patients within the JTTR and DoDTR and then the actual physiologic presentation of hemorrhage, which meant shock or requirement of thoracotomy or laparotomy, occurred in over 2% of patients within the DoDTR and JTTR.

This is probably an under-representation of the injury pattern because it didn't include Armed Forces Medical Examiner's office or those who were killed in action. Nonetheless, it was an effort to try to put forth definition in a structured study of noncompressible torso hemorrhage; what is this?

This was the paper, landmark paper, by Eastridge that did include Armed Forces Medical Examiner's data, "Death on the Battlefield." And now over a 10- or 11-year period, what Brian and his colleagues showed was of roughly 4,000 deaths on the battlefield, KIAs, there were the majority, about 3000, were non-survivable. However, 976 were deemed, by an expert panel, to have been potentially survivable. There was no lethal head injury, cardiac wound, or body disruption. They simply died of hemorrhage in most cases; 91% of those, 888 died of hemorrhage. If you look at where the

hemorrhage was in those 888 patients who had potentially survivable injury, the vast majority was in truncal.

So this is -- doesn't show, project really well, but the vast majority was truncal hemorrhage. And one sees here that junctional hemorrhage, this is really one of the first papers with junctional hemorrhage, was really well characterized in a large number of patients, and then extremity hemorrhage. So these were the potentially survivable injuries from hemorrhage in the "Death on the Battlefield" paper from Eastridge, again showing the implications of truncal hemorrhage.

The second thing, in addition to reviewing the importance in context of hemorrhage, I would like to put forth a modern device categorization. We can debate this over the day, and I think we should. Tony Pusateri and others who are here from our program -- Sylvain Cardin just walked in -- have heard us talk about this. I think that we need to categorize devices as they impact bleeding, and I think the first is a familiar category of exovascular. This is really -- exovascular devices are those with or without adjuncts, such as tourniquets, clamps, compressive bladders, or topical hemostasis. Exovascular means the bleeding is controlled from outside of the blood vessel. It's amenable to pressure.

Really, it's important because it's basic, it's non-invasive. It can be used by medics readily. However, it provides no inherent circulatory support, and there may be even some devices that maybe impede circulatory

support depending upon -- but we need to understand what we're talking about and what category exovascular is, in order to study and develop, I think, smartly in the mid and long term.

The second category is endovascular. This is more complex. It's invasive, it does require some sort of access to the vascular system. The adjuncts are really covered stents, balloons. You've seen this, this is really -- this is endovascular catheter-based technology that stemmed from the management of vascular disease, coronary disease primarily, aneurysm disease and such. Atherosclerotic occlusive disease. And so this importantly -- the endovascular category provides the ability to offer immediate circulatory support. So unlike a tourniquet or a direct compression device in the exovascular category, which isn't going to provide any cardiovascular support, the endovascular category has that potential. And I think we need to separate these, again, not as competitors but as part of a toolbox that can be offered.

The next several slides, I'm going to show examples, representative examples, of these. And these products will be talked about, these devices and others. These are simply a few that I have put together to discuss over the next day or two. Exovascular, this is a familiar picture of a tourniquet, which is an exovascular device. This is a familiar topical hemostatic agent used as an adjunct for compression. One can see this is clearly exovascular. This is a newly developed device designed to control

bleeding from a confined or tract wound. So, again, exovascular, from outside of the blood vessel. This is a device that has been put forth for exovascular control of junctional femoral hemorrhage, as has this. This is a bladder device that supports the pelvis, and the bladder sort of inflates over the junctional femoral region, again to control from outside of the blood vessels, bleeding from the pelvis and femoral region.

This is a device that has been -- it is intra-peritoneal. It's an expanding foam that's designed to provide external compression of bleeding vessels or solid organs within the peritoneum. So although it's intra-peritoneal, it is an exovascular device. It works with the principle of compression from the outside.

As we look at the endovascular, the second category, I found this quote in the last couple of days. Actually, there were a couple of our Russian surgical colleagues from the War Academy in St. Petersburg at the Military Health System Research Symposium recently, and one of them gave me a textbook from Professor Nikolay Pirogov, who was a founder of field surgery in the Russian military. And over a century and a half ago, he said, "A new era for surgery would become, if we will be able to stop the blood flow in a major artery without exploration, external compression and ligation..." And really he was forecasting, I think, endovascular, the endovascular era, which is remote access to a blood vessel through access at a different site of the body, shown here as a balloon that's placed in the thoracic aorta from a

femoral approach, is a schematic.

Endovascular devices allow one to approach, for example, this high carotid artery injury with an arteriovenous fistula. This patient was treated, actually, in Iraq. Had a large Zone 3 hematoma right up under the angle of the jaw, had a penetrating wound that went through the carotid artery and the jugular vein. So this can be explored with an open operation, and it's very difficult; there will be a lot of blood lost.

You see, one sees an arteriogram here that's performed through a 6 French sheath in the femoral artery. You see the carotid artery filling, but immediately the jugular vein fills. So it's an arteriovenous fistula. But instead of putting this patient through a large operation, my colleague, Andy Bowser, did this in 2006 or '7, placed a covered stent over the carotid injury, sealing the fistula and allowing this artery to be managed without a large operation. So endovascular.

This is a missile wound that has gone through the right axillary artery, junctional artery, right? So this would be a difficult place to expose; there's a large hematoma. This patient had an injury severity score of 50, had had a thoracotomy, a laparotomy, and had a femur fracture. So we could have operated on this patient and lost another bit of blood, but certainly to use endovascular techniques, cross this with a wire, and then use a covered stent, saved this patient a significant amount of morbidity. So these are examples of the endovascular category of hemostasis. And, again, unlike

external compression or the exovascular category compression, endovascular occlusion can provide immediate circulatory support proximal to the balloon. So, as soon as the balloon is inflated, one can see, then, the after-load is increased and pressure is improved. The most important things are the coronary orifices and the brain, right, in an exsanguinating patient, at least initially.

Inflow control is distal to the balloon occlusion, and then it's particularly appealing, has less-invasive approach where remote access to sites of torso hemorrhage -- which require an extensive exposure to do in an open operating room.

Some examples of endovascular devices are shown here. This is a Jim Manning paper that he wrote in *Special Ops Medicine* at the end of last year, looking at endovascular resuscitation techniques in devices. He published this, I think, notably in the *Journal of Special Operations Medicine*. Some people say this can't be done by medics and shouldn't be. Jim is a colleague and an emergency medicine physician who is looking at arterial access in the prehospital setting. Shown here is a depiction of a balloon catheter that's inflated from the femoral artery. This is selective aortic perfusion, actually, here. So you can occlude the aorta and actually perfuse through this end of the coronary orifices and the brain. This is an example of one -- one example of an endovascular device. Pryor Medical is also developing balloon technology that's aimed at reducing the catheter size,

that facilitates arterial access, and eliminates the need for fluoroscopy or x-ray to place these devices and control hemorrhage and resuscitate the patient.

How are we doing with this endeavor? Well, this is the cover of this month's *Journal of Trauma* military supplement. This shows gap resolution. This data was presented to the Senate Armed Services Committee as a follow-up of our research program and shows that in 2008, gaps were reviewed as being only 9 or 10% closed or resolved within combat casualty care, and a survey or expert panel really views these gaps as now being 39% closed in 2014. So there has been progress in resolving the guidance for the development of the force gaps that was issued by Secretary Gates at the time, in 2008, including hemorrhage control; but the job is far from complete. And I think this workshop will go a long ways to pointing that out, both the progress and the job that still needs to be done, and I look forward to participating in that.

So, to conclude, vascular disruption and hemorrhage result in shock and challenge care of the injured patient. The burden of injury and requirements-driven programmed research have been defined, have really defined hemorrhage and honed devices like never before. So there's the wartime burden; I want us to keep that in mind as context as we discuss these devices in the coming hours and day. I really think devices should be categorized and considered and studied and innovated as either exovascular

or endovascular. Help us do this smartly and in a way that we can understand and categorize them. And, again, the devices are complementary; they're not competitive, in my view. They all contribute to a toolbox that will be needed for a spectrum of providers, for medics to emergency medicine physicians to vascular surgeons.

So thank you again for the opportunity to be here this morning. I look forward to a great couple of days.

(Applause.)

MS. KUMAR: Okay, at this time I would like to invite our speakers for Session I. So come up to the front table, please. Our objective for Session I is to really define the landscape of the products that we're going to be talking about in a little bit more detail than Colonel Rasmussen described for us with that fantastic opening talk. We're also going to be hearing about the current operational environments that the products that are currently used by end users, trauma surgeons, EMS, and by the military are being utilized in.

Our first speaker this morning will be Dr. David Krause. And Dr. Krause is a Deputy Director in the Division of Surgical Devices in the Office of Device Evaluation in CDRH.

DR. KRAUSE: Good morning, and thanks for all of you being here. As a dad of three girls, two of whom are married to military officers, I'm gratified to see such a wonderful turnout. Both of my sons-in-law have

been deployed, so this topic is -- you know, it's particularly poignant to my family.

So I'm the Deputy Director of the Division of Surgical Devices. I hope I can figure all this technology out. Let's see, no. Yes, hey. Okay.

So I'm just going to try to do something in about 15 minutes that probably should be done in a couple hours, but it's just kind of run through what is FDA/CDRH? Why are devices classified the way they are? You know, what was the goal?

Some of the hemostatic devices regulated by our division -- and we have a lot, and these other individuals up here also have devices that are used for hemostasis. Little quick mention of de novo, and I didn't put it on here, but I'm also going to mention the Q-Sub and put up some references. Since I'm going to go through this pretty fast, if you send me an e-mail -- and at the end, I'll put my e-mail up -- I will send you this talk as an attachment to an e-mail, so just ask and I'll send it.

Little history on the Food and Drug Administration: A lot of people wonder why, when there's a budget crisis and different parts of the government are funded and Health and Human Services isn't getting funded, how FDA winds up being funded. Well, this is the roots of that. FDA's budget still comes through the Department of Agriculture, which is always one of the first ones funded, and the roots of it are the Bureau of Chemistry all the way back in President Lincoln's time. The important data on here besides that one

is 1906 when the Food and Drug Act prohibited interstate commerce of misbranded or adulterated foods, drinks, and drugs. 1938 was when the FD&C Act required new drugs to be shown as safe before marketing, and '62 is important because that was the year that drug efficacy was written into the law; '76 was the year of the device amendment.

So this slide kind of covers the history of why the device amendments came into being and why it was felt that regulation of medical devices was important. Up until this time, only about 16 medical devices were regulated, and they were regulated by the drugs, Bureau of Drugs, and things like sutures, the absorbable hemostats, things along those lines. So, when they started seeing these reports of injuries associated with devices, it felt there was a need, and in 1976 they finally passed device amendments.

What the device amendments did was, first of all, they defined a medical device as an instrument, apparatus, implement machine, contrivance, implant, or in vitro reagent or other similar or related article, including any component, part, or accessory which is -- and there are these two added definitions about the intended use and the intended effect.

So back in '76 to, let's say, the early '80s, the FDA/CDRH part of FDA put together these panels that classified medical devices, and they classified them basically into three groups: Class I, general controls; Class II, general controls plus special controls; and Class III. However, they didn't get everything, and those are what we call today as unclassified devices

or pre-amendments devices. So those were devices that were in existence in 1976 but never got classified. And there are quite a few of those that are actually used for wounds and for controlling bleeding.

So the principal unclassified devices that we regulate in our division are wound dressings for external wounds that are made with chitosan, some combination product wound dressings that include thrombin, wound dressings that include oxidized cellulose or collagen, and wound dressings that include zeolite or various clays. Class I has these parameters that guide us in their regulation. In general, Class I devices are pretty low risk. A lot is known about them, and it's easy to regulate them with what we call general controls. And basically the rules for Class I are as written on this slide, and these are covered in the regulations and are not difficult for the FDA to enforce.

So the principal Class I devices are under these regulations: nonresorbable gauze, hydrophilic wound dressings of which calcium alginate is one of those, which has some hemostatic properties. The nonabsorbable internal gauzes. The manual surgical instruments are 21 C.F.R. § 878.4800, and that includes all the instruments that surgeons use. Or not all of them, but a lot of them, and that is things like the hemostats, clamps, et cetera. The tourniquets that, let's say, a medic would carry in his pack would be under 878.5900, non-pneumatic tourniquet. We also have some products that you can apply compression with that are under medical adhesive tape

and bandage.

Special controls are the thing that FDA tries to apply to Class II devices, and those could be things like a guidance document. And if you look on the FDA website, you'll find a lot of these. And recently we've been writing some of these special controls into the regulation, especially when we grant de novos, and that's been something we've been trying to do lately rather than writing guidance. And, again, they may include mandatory performance standards, patient registries, postmarket surveillance, and other additional factors that we can use to improve the regulatory oversight. Again, special controls help us determine substantial equivalence and also, if clinical data are needed, IDE regulations come into play, and they're in 21 C.F.R. § 812.

Substantial equivalence is sometimes misunderstood. Here's a definition. I think the FDA tries to be as lenient as we can, but sometimes we have to be fairly adamant about intended use and things along those lines. So substantial equivalence is how we determine whether something fits into Class II or Class I. Most of Class I devices are exempt, so we don't see those. Class II, we do get to see those, so we get to make that determination. Again, it's a combination of the intended use and the technology that gives us the ability to determine substantial equivalence.

And these are the types of things that we look at: intended use/indication, the device description, specifications, manufacturing,

sterilization, description of the packaging, et cetera, et cetera, et cetera. Labeling is very important. The labeling is one of the prime factors that's used to determine intended use.

The principal Class II hemostatic devices regulated in our division are the electrosurgical cutting and coagulation devices. While those are not, you know, really apropos to emergency use, they are important for a surgeon's -- recently we did a de novo for an expandable hemostatic sponge, XStat. We wrote a regulation for that. It's 878.4452. I think that was a nice success for the company and for us. I think it was hard work, and everybody was gratified by the outcome. There will be more about that tomorrow. Most current unclassified wound dressings for external use that are going to be for hemostatic, we're currently working to make them Class II.

So the Class III devices also have general controls, which again, are written into the regulations, things like quality system regulation. But there's also the issue that we don't have enough information, we don't know that much about these products. We don't know enough to write general controls, so we feel that it's very important that we have a much tighter handle on these, and so we require a premarket application. And these are, you know, devices that in most cases are life sustaining, so there's a good chance if there's a new product that comes along that's for use in a life-sustaining, life-supporting way, that our first thought is perhaps it should be a PMA.

And the principal products right now that we regulate are the absorbable hemostats, things like Gelfoam, Surgicel, and also tissue sealants when they're for general or plastic surgery indications that we regulate. There are also tissue sealants regulated by CBER, the fibrin sealants, and Dr. Jain will be mentioning those a little bit later.

An important thing, and I think a great benefit to all, is what's been going on with de novo of recent days is the FDA -- it was automatic that if a device was found to be not substantially equivalent, that it went to Class III and it could have been the simplest of all devices, but if there was no predicate and there was no way we could get it into Class II or I, it automatically became Class III, and Congress recognized that as a flaw. And so, in 1997, they said any device that was determined to be not substantially equivalent could submit a de novo application so that the FDA could reevaluate that. And that is what is in 513(f)(2).

But, again, in more recent times, Congress recognized that, you know, not everybody wants to go through this process and not everybody wants to get an NSE letter, and that if you can determine ahead of time that there is no predicate and perhaps this device is something that could be used for an important use, that perhaps we could do it faster and just submit the de novo and skip the NSE part. And so the FDASIA of 2012 made that addition to the de novo. So now anybody can submit a de novo right to the FDA now.

This link will take you to the de novo classification process. It's presently a draft guidance. The last time it was updated was August 14; it was just put up there for comment. If you have something to say about it, you can write in and tell them, you know, read the document, make comments. All products that have been granted de novo applications are at this particular website, and the XStat one, I think, which is of particular interest to this group, is listed here. Again, if you send me an e-mail, I'll send you this talk and you can just link to these. And I checked these links; they worked a couple of days ago.

The way to get early contact, if you have something that you think is interesting and it's something that's going to be really useful, send us a Q-Sub. We'll be happy to meet with you, we'll be happy to send you to the right part of the FDA to discuss this. And this link that's here tells you where you can get information on Q-Subs.

There is also a new initiative by the FDA for early feasibility studies. If you have something that you think is going to need a lot of tinkering to get it just right, it would be really beneficial to talk with our early feasibility folks. I've listed their e-mails on here: Betsy Ballard and Long Chen. I know Betsy's here. I'm not sure if Long is here. But, anyway, you can get that there.

This is a good website, it's Device Advice website, and it has all kinds of how to do a PMA, how to do a 510(k), et cetera. This is my contact

information if you want to send me an e-mail. It's david.krause@fda.hhs.gov. Just send me an e-mail; I'll be happy to send you this talk. I'll leave it up there for a second so that you have time to write it down. But all FDA e-mail is fda.hhs.gov and the person's first and last name, so if you remember David Krause, K-r-a-u-s-e, you can send me a quick e-mail. And I thank you and I thank you for your attention and I thank you for your attendance at this meeting.

(Applause.)

MS. KUMAR: Thank you, Dr. Krause.

And our next speaker will be Dr. Ken Cavanaugh, who is the Associate Director in the Division of Cardiovascular Devices in the Office of Device Evaluation.

DR. CAVANAUGH: Thank you. I'm very happy to be here today to give the perspective from the Division of Cardiovascular Devices. The first question some of you may have is, well, what's the difference between a device reviewed in the Division of Surgical Devices versus one reviewed in the Division of Cardiovascular Devices? That is, in many ways, a good question.

Historically, in some device areas, the review responsibilities have been divided up into multiple divisions based on various reasons, including the technology, familiarity with the technology, and the indications. And hemostasis devices represent one such area. This does present the potential for inconsistency among review practices; however, we try to

mitigate that risk by having frequent communication and collaboration on topics of mutual interest, letting each other know when relevant devices come in to us for review, seeing if we can be consistent as much as possible with nonclinical and clinical testing recommendations and expectations, et cetera. Hopefully, we've been at least somewhat successful in doing that.

From a device overview perspective, I thank Dr. Krause for providing the general background on how devices are regulated and classified. There are some devices regulated in DCD that might be relevant to today's workshop. I listed some of the highest-risk Class III PMA products here. I'm mentioning vascular surgical sealants. Those are similar to the ones that Dr. Krause mentioned, but specifically indicated for open vascular surgical procedures. Closure devices used to close off an arteriotomy or access site for catheter-based interventions, typically by delivery of a stapler or another implant. As well as just other products that are intended for temporary internal occlusion of a vessel during cardiac or vascular surgery.

There are other products. We heard Colonel Rasmussen talk about these, about covered stents used to treat maybe fistula, so there are other products that could be used to stop bleeding. These are the main ones where we specifically look at stopping bleeding as part of our review. There are no regulation numbers associated with these, and really, all these have as their indication just a general procedural use, mainly for planned procedures, nothing really about emergency uses, although, of course, they can be used

by physicians in those cases, if they're warranted.

For our lower risk Class II 510(k) devices, the main regulation that's relevant here is 21 C.F.R. 870.4450 for vascular clamp. We've gotten a lot of mileage out of this over the years, includes a variety of different device types. It includes, at its most basic form, just clamps or forceps intended for vascular occlusion during open vascular surgical procedures. It also includes devices intended to provide temporary external compression of arterial access sites typically without the use of an implant, like the ones I just mentioned.

The last two device types I listed here are probably the ones that are most relevant to the workshop, especially the last bullet. One such device is a vascular shunt used for limb salvage in case of severe limb trauma and bleeding. And the other is junctional tourniquets or clamps used in battlefield or trauma situations. As you've already heard, these are used to stop bleeding, really, in anatomic locations such as junctions where the use of traditional tourniquets might not work as well.

So just to talk about those specific indications a little bit. We have granted battlefield or trauma use indications for the junctional tourniquets. The battlefield-specific indications originally proposed by the manufacturers and for some devices, they really are followed by non-military, just trauma indications. The review of these products for this use has some unique considerations associated with it. We certainly do need to consider

the likelihood of device use under non-emergency situations. Would it be likely to be used in those situations? Is that okay, or are there other things we would need to think about in those cases? And we also really focus on benefit/risk principles here. We apply them to pretty much every review we do, but they're especially important here.

Some of the key considerations that tend to come up are: What are the magnitude and severity of the benefits and risks for the product for its intended population? What are the treatment alternatives, including what is the do nothing alternative? What if the patient isn't treated at all? And what are some appropriate risk mitigation strategies that should be employed here? These may include defining appropriate patient populations for device use, appropriate training for the healthcare providers that will be using the device, as well as appropriate labeling considerations to make sure that the device can be optimally used.

Those are really the main points I wanted to convey, just to close with some thoughts to think about during the workshop and afterwards. I would like to echo what Dr. Krause said and really encourage early communication with CDRH for folks who are interested in developing such products. This can start with just an informal phone call or e-mail describing the product, and we can talk about that. And then we can move on to a formal Q-Submission process where we talk about your proposal in more detail and give a little more tailored feedback to the specific proposal and

device you have in mind.

We really welcome input and collaboration from all stakeholders in this base, including, but not limited to, industry, physicians, and other government agencies. We've found that to be helpful in many ways, but particularly in this device area.

We really think it's important to increase all of our mutual understanding of our respective processes and the impact of all of our decisions. At FDA, we have a certain regulatory framework we have to work in, but we also recognize that there are other considerations that go into device development and making it available: business considerations, reimbursement, procurement, institutional considerations. And we really want to factor that in and make sure that we all understand the impact of some of these variables so that we can facilitate the development, and really the availability of safe and effective devices for the patients and physicians who need them the most.

This is my contact information, if you have any questions. And I think now we'll hear some perspectives from some other centers within FDA.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Cavanaugh.

Our next speaker will be Dr. Nisha Jain. Dr. Jain is a Branch Chief in the Office of Blood Research and Review in the Center for Biologics.

DR. JAIN: Good morning. In the next 5 minutes or so, I'm going to present hemostatic products that are regulated by CBER. Of course, this is not going to be a comprehensive list only because I can't cover that in 5 minutes. But I will present an outline of the products that are of the most interest of this crowd today.

Okay, so this is a simplified, just a very simplified, view of the FDA organization chart and this is just to give you perspective of where we are. CBER is within the FDA in the Office of Medical Products and Tobacco, and it regulates biological products for human use under applicable federal laws, including the PHS, Public Health Service, and the Food and Drug Cosmetic Act.

So this is an outline of the hemostatic products. We regulate combination products, which are in the form of biologics and devices. These are generally adjuncts to hemostasis, commonly known as fibrin sealants. There are certain biological products that may be of interest here. They are currently under various stages of clinical development. To name a few, plasma in various forms, which is lyophilized, freeze dried, or spray dried. There are platelet-derived hemostatic agents, such as Thrombosomes and freeze-dried platelets.

So my talk today is really going to focus on the adjuncts to hemostasis. So let's start with the definition of adjuncts to hemostasis. These are fibrin sealants, at least regulated by CBER, which are indicated for

use in patients undergoing surgery, when control of bleeding by standard surgical techniques such as suture, ligature, or cautery is ineffective or impractical. The point to note here is these are all intended for topical use only on the surface of the organ or tissue as opposed to being on the skin.

So brief review of the development of the fibrin sealants. Since 1900s, the surgeons have reported hemostatic properties of fibrin powder when they used it in operative field. But in 1940s, the combination of fibrinogen and thrombin was first utilized for its hemostatic property. And in the same year there was the development of Cohn fractionation, and with the method for cryoprecipitation of fibrinogen, the first fibrin sealant was developed in 1970. It took over two decades from the development of Cohn fractionation and cryoprecipitation that the first fibrin sealant was developed. But in that same year, the licenses of fibrinogen were revoked by the FDA due to the transmission of hepatitis.

In 1980s, the first fibrin sealant became available in the European markets and then two decades later, and after a conference held with the Uniformed Services in 1998, the first fibrin sealant was licensed in the U.S.

So the types of fibrin sealants that are currently licensed in the U.S. market are consisting of a single component, which is thrombin, which could be of human, bovine, or recombinant reagent. And the thrombin may be used in conjunction with absorbable gelatin sponge. Some of them which

are currently available are Evithrom, which is from human derived, or reagent Recothrom, which is a recombinant thrombin, and the bovine thrombin, which is Thrombin-JMI.

A fibrin sealant can be a two-component fibrin sealant with or without the added components of Factor XIII to facilitate blood stabilization. These two components are supplied in separate vials as either frozen solution, lyophilized powder, spray-dried powder, or as absorbable patch. The two components, they are admixed at the site of application. They are administered by spraying, dripping, or the patch can be left in situ. The examples of the licensed product include EVICEL and TISSEEL; both can be either in the frozen form or in the lyophilized powder. TachoSil and EVARREST are patches which can be left in situ.

So, to support licensure of these fibrin sealants, the efficacy studies in a pivotal clinical trial, the fibrin sealant should be tested in settings and under conditions where they would normally be expected to be used in clinical practice. They can be tested against a placebo, a cleared hemostatic device, or other control, as appropriate. The primary endpoint in this pivotal trial could be either a hemostatic endpoint or other measures of clinical benefit depending on the indication that is being sought.

So the primary endpoint of the studies which support the licensure of fibrin sealants, they're reviewed on a case-by-case basis. So far, for all the currently licensed fibrin sealants, the primary endpoint that has

been used is time to hemostasis. The other endpoints that can be considered based on the indications sought are blood loss, transfusion requirements, tissue sealing, and wound healing depending on the indication for the fibrin sealant.

Fibrin sealant has multiple biologic components, then the contribution of each component, it can be demonstrated in a non-clinical setting appropriate to the indication sought. However, the overall efficacy of the multiple-component fibrin sealant should be demonstrated in clinical trials.

Important safety information of these fibrin sealants, because they are only for topical use on the surface of the organ or the tissue, all package inserts are -- fibrin sealant under contraindication section clearly say that they should not be injected into the circulatory system and they should not be used for the treatment of severe or brisk arterial bleeding. And the warnings and precaution sections of the package insert, there is a risk of air or gas embolism with the use of spray devices employing a pressure regulator.

So, in summary, a number of fibrin sealant products are licensed in the U.S. The safety and efficacy of these products have been demonstrated in adequate and well-controlled clinical trials. They are indicated as adjuncts to hemostasis to control bleeding and oozing from capillaries and small venules. And the use of fibrin sealants to control other

types of bleeding has not been studied in adequate and well-controlled clinical trials.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Jain.

Our next presentation will be from Dr. Nicole Verdun, who is a Medical Officer in the Hematology and Oncology Products in the Center for Drugs Evaluation and Research.

DR. VERDUN: Thank you. So, in the next 5 minutes, I will talk about something controversial. Why not? In the Center for Drug Evaluation and Research, we do regulate some hemostatic products, but they're a very limited number that we regulate, and so I'm going to discuss those and a few clinical studies in particular.

So the Center for Drug Evaluation and Research approved drugs include the antifibrinolytics, and these are used off label. There is no specific indication for use with trauma. Aminocaproic acid, the indication that is listed, is that it "is useful in enhancing hemostasis when fibrinolysis contributes to bleeding." And tranexamic acid, the indication is for the reduction of peri- and postoperative blood loss and the need for blood transfusion in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty. Tranexamic acid is thought to be a competitive inhibitor of plasminogen activation and has some noncompetitive inhibition

of plasmin at higher concentrations. And it has been shown in vitro to be 10x more potent than aminocaproic acid.

The CRASH-2 trial was a randomized controlled trial in 274 hospitals in 40 countries, and this included 20,211 adult trauma patients with or at risk of bleeding within 8 hours of injury, who received, they were randomized to receive, tranexamic acid or a placebo. And the primary outcome of that study was in-hospital death within 4 weeks of injury.

The results of the CRASH-2 trial high-level overview was that all cause mortality was reduced in the tranexamic acid group, and the risk of death due to bleeding was reduced with the tranexamic acid. The survival benefit occurred if tranexamic acid was given within 3 hours of injury. And interestingly, in the study, there was actually an increase in mortality due to bleeding in the tranexamic acid group if treatment was initiated after 3 hours of injury. So the results are a little bit difficult to interpret in that regard in terms of the time limit.

Some of the criticisms of the CRASH-2 trial was that there is a lot of variability in countries with regard to trauma resuscitation and care standards, including blood product use, and so the generalizability of the results is an issue. Only 5% of the patients actually had bleeding as a cause of death in the trial, and there was no data regarding fibrinolysis status on admission. There was also very limited data on injury severity, no data on blood loss, and only 50% of the study cohort actually received a blood

transfusion. And there was just a small number of patients that actually had hypotension or tachycardia during the study. And there was a small effect size; granted it was a very large trial, but there was a 0.8% absolute reduction in death caused by bleeding. And then there was one issue that we actually do look at, which is the lack of systematic AE reporting, so that also brought up some concerns with the results.

Then there was the Military Application of Tranexamic Acid for Trauma Emergency Resuscitation Study, and this was actually a retrospective observational study of 896 admissions with combat injury. And there was a comparison of tranexamic acid administration with no tranexamic acid in patients that were actually receiving either greater than or equal to 1 unit of packed red blood cells. There was a subgroup analysis that was done on those that received greater than 10 units of packed red blood cells. And the primary outcome of that study was mortality at 24 hours, 48 hours, and 30 days and the influence of tranexamic acid on postoperative coagulopathy and then also the rate of thromboembolic complications.

So, in the MATTERs study, out of the 896 patients, 293 or 33% received tranexamic acid within 1 hour of injury, and 125 were in the massive transfusion group, so those that received at least 10 units of packed red blood cells. And in the no tranexamic acid, that was 67% of the patients in the study with 196 in the massive transfusion group.

And a high-level overview of the results of that study: The

tranexamic acid group did have a lower mortality than the no tranexamic acid group of 17.4% versus 23.9% despite actually a higher baseline injury severity score. The benefit was greatest in those that were receiving the massive transfusions, and tranexamic acid was independently associated with survival with an odds ratio of 7.228 and less coagulopathy. There were higher rates of venous thromboembolic events in the tranexamic acid group, but several factors make this association difficult. There were a very small number of events and a higher injury burden, as I mentioned, in the tranexamic acid group. So, again, it's difficult to assay.

So, in summary, for CDER hemostatic agents, which include primarily the antifibrinolytics, they seem to have some benefit in trauma settings. But the exact dosing, the timing, the mechanism of action really do need further prospective evaluation. There is a lot of off label use, while not ideal, but it does allow for use for trauma indications. And the FDA and CDER are committed to the development of such agents, and encourage further study and new exploration. We actually do have some INDs open now that are kind of trying to look at some of these issues, but we welcome more study in this area.

Thank you.

(Applause.)

MS. KUMAR: Okay, I would like to invite our next speaker. We're going to be switching gears now and hearing from our end users about

the currently marketed products that are being used in their facilities. I'd like to invite Dr. David King up for his presentation. Dr. King is a lieutenant colonel in the United States Army. He is a trauma and acute care surgeon at Mass General, and he's also the Director of the Knight surgical research program.

DR. KING: Good morning.

So I've been asked to give a brief overview of existing hemostatic devices and their characteristic use on the battlefield. You know, we always get stuck with this issue of trying to frame this argument; it's been framed very well. War fighters get injured in a variety of ways. It's a little bit different than the civilian world. But once you're bleeding, it's substantially the same. Most of our war fighters are injured by explosion or other missile wound, very few from blunt trauma, but they're out there. But as I say, after the moment of injury, the similarities between the military world and the civilian world are more than they are less.

When you look at where our war fighters are dying, they're dying before they reach a surgeon. So, if you can get to an operating room, your chances of survival are very high, well into the 90% chance of going home if you come to a surgeon with some kind of vital signs. So we do well from the surgery side. Where we fail and continue to fail, despite dramatic and significant advancements in the past decade, is in the prehospital hemorrhage control area. So you're most likely to die before you reach a

surgeon, and you're most likely to die as a preventable cause of death from bleeding. And that's where we should be focusing our efforts.

As a brief review -- and I'm going to try to stay away from the lingo of military echelons of care and try to break it down into a little bit friendlier terms for everyone to digest. In this area we call self-aid and buddy-aid or so-called point-of-injury care, that care is delivered by a medic, a military medic. These are not exact analogies, but to give you a frame of reference, you can maybe think of that person as a civilian emergency medical technician. That's not exactly true, but I think it's good enough for this discussion. An advanced medic, maybe you consider something like a civilian paramedic or perhaps even an advanced trauma nurse practitioner, something like that. And then point-of-injury care is also delivered, in some cases, by doctors, emergency room doctors or emergency physicians, and in some cases, surgeons as well.

As you move up the echelons a little bit, care can get slightly more sophisticated at this so-called first responder battalion aid station level. But, again, the providers there are medics, advanced medics, and sometimes a physician, usually not a surgeon.

And then at the forward surgical team is -- generally the first time, unless you're in this fortunate group at the point of injury where a surgeon is available, but largely, for most war fighters, the first time you see a surgeon is at a forward surgical team or similar -- that's an Army term -- or a

similar facility in one of the other branches of service. That's the first time you see a surgeon. And if you can make it to that point in your care, the chances of going home are well over 90%.

A CSH or a theater hospital, you can -- most people largely regard this as similar to a civilian-level trauma center. It's not exactly true, but again, for framing this discussion, I think it's a reasonable analogy. The resources at a theater hospital are extraordinary, and as every year goes by in this conflict, those resources become more and more and more unlimited.

And then, of course, definitive care delivered back in the United States.

But the effort -- and I think the discussion occurring today and tomorrow is largely devoted to care at the point of injury. And this is, of course, the area where we can make the greatest difference. Now, care at the point of injury is dictated by a doctrine we regard -- or a doctrine, military doctrine, that's called Tactical Combat Casualty Care. That's generally broken down into three phases. It's fundamental, for this discussion, to understand what we could do at those phases of care at the point of injury. And again, remember, this is the point where we can make the biggest difference.

So the first phase of Tactical Combat Casualty Care is called Care Under Fire. This is largely misunderstood. What can we accomplish during Care Under Fire? The first rule of Care Under Fire is to return fire, right? So as not to sustain additional injuries. We determine if the casualty is

alive or dead and provide hemorrhage control. That is largely it. Notice you don't see a lot about checking airway and breathing and circulation. There is -- generally, no CPR is administered. If a casualty is pulse-less during Care Under Fire, then they're probably non-salvageable.

Now, it's easy to talk about this, but trying to really understand it is quite a bit more difficult. So I'll play this video for you, which is an example of Care Under Fire. And it's not meant to scare you; it's meant for you to understand what the limitations are for providing medical care at the point of injury.

(Video played.)

DR. KING: So he is reaching for a hemostatic device.

(Video continued.)

DR. KING: And you'll notice he has a junctional wound that's getting packed with a hemostatic device.

So those 3 minutes of time I just ate up to show you that, I think it's a worthy investment because, to me, it's difficult to sit here behind a desk and with podiums and coffee and propose to dictate how we're going to deliver care on the battlefield without understanding the limitations that our war fighters are facing at the point of injury. You'll notice nobody put on gloves. That guy is sitting in a pile of mud and dirty water, so I think you understand the issues.

After Care Under Fire, which is what you just saw, is the phase

of care called Tactical Field Care. Now, if you back up to Care Under Fire, you'll notice that hemorrhage control is on there. Well, hemorrhage control during Care Under Fire largely means extremity and junctional hemorrhage control. Under Tactical Field Care, we can get a little more sophisticated at the point of injury; that is open airway, we treat pneumothorax. We continue to treat ongoing junctional and limb hemorrhage, and at this point, we can start to provide some fluid resuscitation or blood loss, critical blood loss replacement.

But our war fighters are dying for a lack of intracavitary hemorrhage control. And this is, under Tactical Field Care, would be the ideal timing for creation or for intervention for intracavitary hemorrhage, but there are no interventions. And, again, there's no CPR here. And during Tactical Evacuation Care -- so that is movement of the casualty from point of injury to more definitive care. Really, all we can continue to do are the same sets of skills, that is ongoing fluid resuscitation, junctional and extremity hemorrhage control, and there are no intracavitary hemorrhage control maneuvers. And at this point, you can start to consider intervening with CPR.

The hemostatic dressings, there's a whole variety of them. I think the only important thing to understand here is that this started as one idea a decade ago and has developed into a whole host of tools in the toolbox to help the war fighters. There's a variety of them, and they're being used in all manner of ways, some intended, some not intended.

Probably the single greatest life saver and the single greatest intervention that's resulted in lives saved on the battlefield in the last decade is the tourniquet, and the science clearly bears that out. Someone -- well, a few people have already mentioned the role of junctional tourniquets and the innovation that's taken place for the non-tourniquetable exsanguination.

And, of course, we're going to hear all about the evolution of XStat. And this casualty, you can see how the junctional wound that may or may not have benefited from use of XStat, but at the time, the only thing you could offer this casualty is packing with the hemostatic bandage.

The so-called battlefield design requirements. So they're not that different than you would envision, for a rule, civilian emergency medical practice. Naturally, electricity is a problem. You can see those guys are not carrying around a generator or a vehicle with generator; they're on foot. We have to be able to tolerate temperatures and changes in pressure and humidity, variable weather. It certainly has to be ruggedized, it has to be able to sit in a backpack and get banged around for months on end. And it goes without saying that low weight and cube are paramount. No one's going to carry something that weighs 100 pounds on their back on the off chance it gets used every now and again.

This is a summary of other, what we regard as hemorrhage control interventions available in the prehospital arena and whether you regard fluid resuscitation or permissive hypotension as an intervention. What

I would say is that's not a hemorrhage control maneuver; that's prevention of creation of worsening hemorrhage. That's different than a hemorrhage control maneuver. TXA, prevention of hypothermia and coagulopathy and so on.

The overarching principle for what we can carry forward now to the point of injury where we can make the biggest difference is this, right? It has to fit in a backpack. It has to be small enough and lightweight enough and robust enough that our guys can carry it forward so that we can make the biggest intervention or have the biggest effect size where our war fighters are dying, and that is in the prehospital environment. And they're dying from hemorrhage, largely noncompressible torso hemorrhage, and we need to keep our eye on that part of the ball in terms of this discussion in this meeting.

Oh, with regard to surgical intervention, everyone gets back to this. I think it's largely beyond the scope of this discussion, right? As I said two times and I'll say it a third time now, if you can get to a surgeon, as a war fighter, your chances of going home are very good. This picture of the bilateral lower extremity amputation is just a demonstration that we're using hemorrhage control devices even at this sort of role to forward surgical team. They're everywhere. But that's not where our efforts should be directed.

And in case anyone is in doubt about the similarities or differences between civilian trauma and military trauma, this was us in

Boston just last year, and what I would say to you is yes, there are differences, but there are also a lot of similarities. One of my patients here with the lower extremity amputation, that could be a battlefield wound. And I'll also point out that that same patient underwent a laparotomy for noncompressible hemorrhage for which we have no prehospital intervention right now that may have benefited her, not to mention the rest of our war fighters.

Thanks.

(Applause.)

MS. KUMAR: Thank you, Dr. King.

Our next speaker will be Dr. Rick Alcorta. Dr. Alcorta is the Director of Emergency Medical Services.

DR. ALCORTA: Greetings. It's my pleasure to try and give you an orientation from a civilian perspective on hemorrhage control and what I view as truly preventable death. The realities are we live in a society that has accepted traumatic death as a fait accompli; it's an accident. That is not true. These are preventable deaths. And we haven't necessarily focused the energy, the cost, the dedication to preventing the preventable death. This is one of our opportunities to do that.

Very clearly, the CDC has reported that we've had over 181,000 traumatic-related deaths in a year. The National Highway Traffic Safety Administration for motor vehicle crashes in 2010 reported there were 32,000

deaths and over 2 million injuries. And the interpersonal violence that we hear about on a daily process, on our reports, count for 20,000 deaths, and falls -- yes, "I've fallen and can't get up," the classic line, but the reality is those falls can be very significant and cause death 31,000 times a year.

So we clearly are at risk, and we look at road injuries, it's the fifth leading cause of death nationally in the United States. That is behind heart disease, lung cancer, stroke -- I'm sorry, lung cancer, stroke, and chronic obstructive pulmonary disease. Now, the citation that I have at the bottom is a wonderful reference that was just published May 2014. It's on the National Highway Traffic Safety Administration's review that very clearly addresses the efficacy of prehospital application of tourniquet and hemostatic dressings. And the cornerstone of this whole process is there's very little EMS good prospective data. And the sad part is, is tourniquets have been being used for hundreds of years, and we still have folks that are questioning its utility.

There was an analysis done in 2011 looking at the national trauma database, and between 2002 and 2005, 2.8% death rate of patients with an isolated extremity trauma, isolated -- it's not junctional, it's not in the axial in the groin, it's an extremity injury. Totally preventable. And among the same set, 6.5 suffered an amputation of some type. Those are, in my mind, truly preventable deaths by some of the techniques we're talking about here today.

How can we make a difference? Current issues in EMS center

around the fact that we have folks that don't read the literature. We have EMS providers that are excited and are very gadget-oriented, they like the new-fangled thing whether it's validated or not, they like the new thing on the market. It brings me concern when I have folks that say it's direct pressure and direct pressure is the only way to control the wound and tourniquets are a last resort. I disagree with that.

I think if you got an active hemorrhage, you should put a tourniquet on because we can get you to definitive care in a timely fashion in most settings. Most. Very clearly, we have some rural areas where it's three to 4 hours, or in some cases, it's waiting for an airplane to come in the next morning to ship you out. But those are more the exception than the standard rule. And there are a few folks that believe in "anti-tourniquets." I disagree with that also. And we need to change that. Very clearly, the military and civilian transport times may be different, but in a civilian sector, we have hospitals and a lot closer than many of our military folks do. So we should be able to use a device that has a limited risk of secondary injury and use it effectively to save lives.

Very clearly, when we look at this, the tie-down pressure dressing, I'm not a big advocate of. Because what that means is I put a gauze on and I walk away from it. And if I don't have true hemorrhage control, it just means I'm going to put another on and another on; meanwhile, I have an inch of blood in the back of my ambulance and the patient is nearing, if not

in, cardiac arrest when they arrive in the emergency department and in the trauma resuscitation bay with me.

Now, there are some spectrum of products that are out there. You've heard of many of them here, and they center around powders, gels, impregnated dressings; they are an adjunct, but not the solution. That requires direct pressure and direct supervision by an EMS provider, and when it gets to definitive care, they need to be able to remove that material to get exposure and then approximate control.

Regrettably, we still have some doctors in EMS that are not terribly knowledgeable about the literature, as well as about what are appropriate protocols. This is a challenge. The good news: Again, the National Highway Traffic Safety Administration has taken a lead and has put together a grant process to try and establish national EMS guidelines. This is a huge step forward because if you look state to state, there are only about 15 states that have statewide protocols that EMS providers must comply with, many of which may comply with, which means they can do what they want. And in some states, they have as many as 64 different protocols managed by different EMS medical directors and services. A challenge, a problem; we're trying to address it. But it centers on the need for leadership from those that are trying to approve, recognize, and authorize the use of certain devices and techniques.

We don't have a good IV pro-coagulant/oxygen carrying

alternative to whole blood that I can take out to the field. We're in the crystalloid realm, maybe Hetastarch. That's about the best we've got out there. Those volume expanders are just that, volume expanders. They don't meet the ideal needs -- and I'll touch on that in the next unmet section -- but that becomes an important piece, and we're looking at some of these alternatives, such as lyophilized freeze-dried plasma. It's promising but clearly is not FDA approved for use here in the United States. So we need to look at those.

So I'm going to come back to the tourniquet and the concept. They've been around for years. The reality is, there are the caveat or provider-made ones that are not ideal. One, they are frequently not put together in a just-in-time fashion very effectively and may or may not do the job as they need to. I support manufacturer or vendor-based devices, but there's a slew of them, some of which when you take out and apply pressure to break before they get hemorrhage control. Not a good tool. But those that work and work effectively should be the standard of operation.

This is what we're advocating now for active shooter scenarios where we're talking about what are called IFAK kits, Individual First Aid Kit, which are designed for buddy care. This is for care under fire; it's a model the military has used, model that our law enforcement should be carrying, as well as our EMS providers. And it's not one, but two tourniquets should be part of that kit. Why? Because they're not going to give up theirs to take care of a

civilian. So we need to make sure we're preparing our folks in an active way to address this.

The timely application and transport issue is important. You need to get immediate control of active hemorrhage. Sorry, immediate. Because I want my patient to arrive as a Class I ATLS hemorrhage, less than 750 cc, rather than getting them there, say, well, doc, I tried pressure dressing, didn't work. I went to an impregnated gauze, didn't work. Oh, yeah, and I got to a tourniquet. Meanwhile, I've lost another liter's worth of blood.

So now we've taken a patient from maybe a Class I hemorrhage and put them in a Class III hemorrhage. By the time they resuscitate, their coagulation factors are gone or at least depleted. We need to have the ability for folks aggressively to manage that, get them to definitive care where they get proximal control and save these people's lives. Again, not like the military; we're able to move them much more readily, much more quickly to definitive care. And we look at the complications of a device, which you always have to do. Risk/benefit ratio. We want to look at what likely are we to injure.

Good studies. Several put out by Beekley, Dayan, Kragh, and Lakstein really validate that these are non-life threatening complications, and most of them are reversed upon removal of the tourniquet and proximal control. These are not necessarily permanent long-term findings when we're

looking at this.

So what we want to basically try and do is look at the devices. Now, here's a challenge for any EMS operational program. Every one of these programs across the United States is fiscally challenged, you know. I can't spend millions of dollars to outfit my ambulances to meet an incredibly rare event. And the way I say that is junctional injuries in the United States are not common. Combat setting, more common. Absolutely. And, therefore, the timeliness -- is that person going to be alive by the time EMS arrives 15 or 20 minutes in moderate transport locations, not urban centers -- a junctional hemorrhage, femoral, axillary, without control. They're probably not going to be viable at the time they arrive, let alone with this nice fangled device.

The other is the cost. I'm Maryland. I've got over 750 public safety ambulances and 442 commercial ambulances. Do we stock them with an expensive device that they will probably not use in decades? So we need to make sure we have the right tool, cost-effective tool to meet a need. Is it the right one and the right process?

Hemostatic agents. Very clearly, we've got some pre-release data. They were approved. And as you've heard, there's a spectrum of them out there. The challenge is the post-release monitoring maybe could be stronger, and we could be interfacing better, looking at the National EMS Information System, called NEMSIS, data collection tool, and the National Trauma Data Bank, the NTDB. Well, we found, retrospectively, untoward

events with exothermic reactions with the powdered original formulas, and we then realized maybe not the best thing to pour in an open wound.

And even today, literature demonstrates, in the last decade, we still have an exothermic reaction with powders or granules, and there is pain associated with it and some burning. So we need to be having an ongoing process to monitor, both premarket, postmarket, and not just anecdotal untoward event reporting, but a prospective, integrated process so that EMS medical directors and state medical directors like myself, who establish statewide protocols, can say this is the right device, this is the right intervention, because it has the most benefit, best bang for the buck, and this is the training that we need to establish for our providers.

In Maryland, we've removed pressure points and elevation. Basically, it is direct pressure. If you can't control it immediately with direct pressure, you go to tourniquet. That's Maryland's protocol for an entire state. But I can't tell you that's the way it is for all states. And that's only because we have a dedicated state medical director, essentially 24/7/365, trying to make sure that we're as current as we can with standard of care. And we have the authority to influence the education of our providers within our system, and we need to do that.

We have some of the new tools that are out there, an old concept: wound packing with some new twists. Sponges, et cetera. Different types of gel, sponges, that are available. Very good in confined spaces, as you

heard in the military model. Same issue. When we start looking at intra-abdominal/intrathoracic, we've got a challenge. We have a void still there. I'm not about to have my paramedics put in an intra-aortic balloon to get proximal control. Sorry, it's not going to happen; at least not today, with the technology we've got. We need postmarket managing to make sure these tools work and work effectively.

So, in summary, I think, one, we've got to improve the education of evidence-based recommendations that are out there. Part of that is being done by the National Highway Traffic Safety Administration and the Federal Interagency for Emergency Medical Services, called FICEMS, in an effort to standardize and basically improve, bringing everybody up to a level of the best evidence that we have, some of which is anecdotal because there isn't a lot of quality EMS research that's been done in a prospective fashion. It's very difficult to do that.

Next is, clearly, tourniquets save lives. They should be used much more aggressively, much sooner. Junctional tourniquets clearly have a military role, but there's also a place for it in the civilian sector; but it needs to be done effectively with good monitoring in a cost-effective fashion. Hemostatic agents, excellent tools with impregnated gauze, because it's not just pour in wound and hope it cooks, because that's what it will do. We don't want that. And then the injectable sponges, the data is coming. We're still not quite there. So until we have a tool that does all those things

effectively and we have a resuscitative fluid that is a pro-coagulant and oxygen carrying capacity tool, we have a real challenge. And that's where I look to the future, and I'll cover that in Unmet Needs.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Alcorta.

Our next speaker will be Dr. John Holcomb, who is the head of the Division of Acute Care Surgery at the University of Texas Health Science Center in Houston. He is also the Director of the newly established center for the Center for Translational Injury Research and also had a distinguished career as a colonel in the United States Army.

DR. HOLCOMB: Well, it's a great pleasure to be here today. Thank you very much.

I'm going to probably summarize some of the things that have been said already. Injury is a big deal. The *Journal of Medicine* published this. It's the leading cause of death around the world, greater than HIV, tuberculosis, and malaria. And interestingly, and not due to war, is increased by 24% worldwide. In Peter Rhee's paper in *Annals of Surgery* just 2 months ago -- you're not going to be able to read this, but look at the blue bars. At the bottom there is cancer and heart disease going to the left; that's good. And injury is the top right-hand one, it goes to the right; that's bad. So just like in the *New England Journal of Medicine*, injury, death has increased in the

United States over the last decade by 22% while cancer and heart disease has gone down.

Many hemostatic devices, and most of these have been discussed already, across the top are tourniquets and junctional devices. I am conflicted with one of these devices; I helped invent one and -- you know, in our efforts to help stop bleeding. Tourniquets, hemostatic dressings, REBOA, Colonel Rasmussen has mentioned already. There's hemostatic foams, the fix the flat, so to speak. And across the bottom are the injectables that have been discussed. So lots of different options out there. I would say that there's a dearth of great data.

Why are we here talking about this? This is a guy I took care of this year. I had a lot of opportunities in the military to take care of gunshot wound patients; there are a lot of these in the civilian world as well. This guy had a thoracoabdominal gunshot wound. This is the next day, because we didn't take pictures the first day because we were busy stopping bleeding. Took out a lot of his liver, part of his lung and his kidney. He ended up pretty sick but went home in 30 days. These people die unless they're in really, really high-level quality centers around the country, and there are a lot of them.

So the need, as has been described -- and I'm going to show some data documenting this need -- is really to help stop truncal bleeding. The risks are very, very high. When you read the FDA language, they talk

about risk and benefit. Risk and benefit. So the risk is really high. Trauma laparotomy, at the best trauma centers in the country, has a 30% mortality risk, 30%. Not many people really realize that. It's well documented in the literature and in the national trauma databases.

Postmarket approval clinical data should be required. I'd like to know if these things work, right? I'd like to know. They're out there, there's no requirement for postmarketing data. I'd like to know before I go put them on my helicopter or use them in the ED or train the medics in Houston, where I work right now, just like was said already, and I would like to have known when I was taking care of guys out on the battlefield.

We need some clinical data. Now, you've got to be careful, okay, because this isn't heart disease where the budget is $7 billion for heart disease at the NIH and they can do studies of 20,000 people. That's not the world we're living in. You guys know that. We can't fund those studies because the budgets aren't there to do it. The device companies, for the most part, can't do these. So efficacy and safety, risk and benefit, and the appropriate endpoints must be taken care of.

I'm just going to show some of the opportunities and a little bit of the conundrum with data. This is a DoD-sponsored study, $10 million. We put people in the EDs to record what was happening at 10 trauma centers across the United States, published it a little over a year and a half ago. Twelve hundred patients received at least a unit of blood products in the first

6 hours after admission. You can see the 24-hour Kaplan-Meier. Again, this is just observational data. Twelve percent mortality over the first 24 hours. Most of the mortality occurred in the first 6 hours. So these are people who got red cells in the first 6 hours -- and oh, by the way, 184 laparotomies within 64 minutes out of 1200 patients, or 15%.

Twenty-five percent mortality out to 30 days. You can see most of the action occurs very quickly. So what caused the deaths? The other deaths are head injuries. This is a little bit of the conundrum from a regulatory point of view is, we're focusing on hemostasis; you've got to do that and stop bleeding. But, in fact, a lot of the patients die of head injuries, and they do that later. Later. So having 24-hour and 30-day mortality as endpoints of these hemostatic devices is extremely difficult.

Now, the PROPPR study, just completed. We enrolled 680 patients over about 15 months. We screened 11,000. A lot of them got massive transfusion. A $52 million study, pretty expensive study. What you can see in this group is much like the Kaplan-Meier showed previously: most of the death occurs in the first 3 hours. The enrollment criteria here is at least a unit of red cells in the first 2 hours. So we move that time period closer, the slope of the curve is steeper in the first 3 hours rather than 6, but you still end up with that 15% mortality. Now, half the patients get laparotomies. Half the patients get laparotomies for truncal bleeding. And, interestingly, at 30 days the mortality is almost exactly the same. Higher

initial death rate from bleeding, but the final mortality is exactly the same, and it's the head injuries that cause that later mortality to be the same.

This is data from our center. One of our medical students went back and looked at deaths in '05 and '06 and deaths in 2012 and '13. A thousand deaths, got a lot of trauma patients coming in, in Houston. And, unfortunately, a lot of them die. And you can see that the death is almost all -- happens in the first day. And if you explode out that first day, almost -- the majority of the deaths occur in the first hour. Now, this doesn't have prehospital data associated. This is people who live long enough to come in to the ED. All the action occurs very, very early. So, if we're going to have an endpoint, I think it should be very early and then have secondary endpoints to take care of the things that happen later.

Cause of death is heads and hemorrhage. Heads and hemorrhage over and over and over again. So from an epidemiological point of view, the data are conflated or confounded by head injury. So we're talking hemorrhagic deaths and hemorrhage control and effectiveness and safety, must consider in some way these head deaths that are all in here. Now, the problem is that you can't get a CAT scan before you rush a guy to the operating room and stop bleeding. So from a study design point of view -- and I know the study design people are going to have a heart attack at this point -- post hoc must be excluded or you can't do these studies with current technology. That really is the conundrum we're in right now.

So entry criteria, of course, with any study is really important. You can change your criteria, you can increase or decrease the deaths in the first 3 to 6 hours. Most patients have both heads and hemorrhage as a cause of death. And the laparotomy thing, well described. John Clarke did a really, really nice paper, published this in 2002 in the *Journal of Trauma* where they documented the mortality from truncal hemorrhage in the Level I trauma center in Pennsylvania was 40%. Interestingly, there is a time element well described in this paper. For every three-minute delay to the operating room, mortality increased 1%. So there is an absolute relationship with time and mortality. Data from the last two years, National Trauma Database, and then individual trauma centers, as we started, coalesce around truncal hemorrhage, document this 30% truncal death rate from laparotomy at leading Level I trauma centers.

The clinical need. You know, here's our current plan: Get to the OR quickly. That's the current plan. It was exactly the same in 1985, when I was an intern, and I teach the interns and the residents today exactly the same thing. You can't get there any faster than about 10 or 15 minutes, once you're in the hospital; it's really hard to do. Some places get there a little faster, but not much. And so our interventions in the hospital in a disease has a 30% mortality, hasn't changed appreciably in 20 years, is run to the operating room faster. That's our solution. And, ladies and gentlemen, I think, as a group, that's why we're all here. We want to decrease that with

new technologies because they are desperately needed to reduce mortality; again, that benefit and risk issue.

What have we done in Houston? After I got out of the Army, six, seven years ago, is we put tourniquets and hemostatic dressings, junctional hemorrhage control devices, red cells and plasma, ultrasound, blood warmers on our helicopter. Our medics and nurses use these routinely in 3,000 missions a year. They're capable with LVAD and ECMO. These guys are really good, they are equivalent to military paramedics in some special operations units. We are really fortunate to work with them. If we had a new technology, I would start it in the ED in the hands of trauma surgeons to make sure it works and then rapidly transition it to those guys prehospital because that's where we know that the biggest bang for the buck is.

Level I centers, just to remind everybody, have a lot of capability and a lot of people. There are only about 200 Level I centers in the United States out of 1200 trauma centers out of 5,000 hospitals. The literature clearly documents for equivalent injuries, your survival is greater in a Level I center. The problem is there's not many of them. There's not many of them. So the vast majority of people in the United States get taken to non-Level I centers.

We talked about REBOA already. We're using this in our ED in the hands of trauma surgeons. So you come in with a guy who's about to die, you make an incision in the groin, stick a catheter in, roll the catheter up into

the aorta and blow up the balloon, rather than making an incision this big in the chest to put a clamp on. It's a pretty radical maneuver to do without fluoroscopy, but these patients are really, really high risk. This group probably has a 60-70% mortality. They're the sickest of the sick. So we're willing to take, as clinicians, risk and benefit already with this procedure. Risk and benefit. We want new devices to help us.

There are a lot of bleeding patients. So those two studies that I discussed earlier cover about 60,000 patients, about 1700 enrolled into those two studies. And that was just at 10 centers, 10 trauma centers, in the United States. Very high risk. Majority of these patients in the United States go into non-Level I centers. I think, as we roll out this technology, there needs to be rigorous training in force before the devices hit the street and then postmarket approval data.

And in some way -- you know, I worked in a federal agency for a long, long time. This is a dangerous thing to say. You guys need to be a little bit more strict on some of these devices and generate postmarket clinical data that we can then utilize in a rapid fashion, right? Not 10 years later or 5 years later, but pretty quickly to figure out if we're going to see a risk or a benefit. And I say that just so that we can then disseminate that through our academic institutions through all of our societies. Thank you very much.

(Applause.)

MS. KUMAR: Thank you for that excellent talk.

We will now begin with our, what I'm sure will be very robust, panel discussion. The moderator for our panel discussion will be Dr. Howard Champion, who is a Professor of Surgery at the Uniformed Services University of Health Sciences.

DR. CHAMPION: Thank you.

Welcome, everybody here this morning. I want to thank the FDA for causing this group to come together. You've heard about the extent and nature of the problem, the fact that over 5 million people a year die from hemorrhage, that there is a significant fraction of those that are preventable deaths. This is global data. And what happens here in the next day and a half will begin to affect all of those individuals.

John Holcomb here provided huge leadership during his time as the trauma advisor to the Surgeon General of the U.S. Army and has laid out the landscape of current understanding of early death from hemorrhage. It is now moving from the military setting into the civilian sector, again, with his leadership in the studies that he identified. I think there's no doubt that we've got an early death problem from hemorrhage and that significant steps can be taken to address some of these issues. And it requires a collaboration of everybody in this room, both government and non-government.

So one of two points that I think we want to extract, before I open the floor for discussion, is the transportability of data. You've heard from various individuals that data acquisition early post-hemorrhage, and the

ability to conduct structured scientific studies, is a formidable challenge. Therefore, is there any upside of transporting data from the military to the civilian sector, from bleeding in cardiac surgery and orthopedic joint replacement into some of the datasets that might be required to look at approval of devices and various drugs that might affect the management of early hemorrhage?

So, John, would you like to comment on that, because you've straddled the civilian and military section? And the mortality from cardiac surgery is way less than it is from liver bleeding that we saw, trace that you gave us.

DR. HOLCOMB: Yeah. So cardiac surgery is inherently very different than somebody who is accidentally hypothermic, coagulopathic, and acidemic. I think there are some things that we can learn, but what I'm struck when people ask that question -- and we just use the data that's already available. There are many more bleeding-to-death trauma patients around the United States, I think, than elective cardiac surgery. So I would say no.

DR. CHAMPION: So the cardiac and the bone surgery for TXA studies are not particularly relevant, we think.

DR. HOLCOMB: Yeah, the TXA studies are very interesting. The TXA and the prospective randomized orthopedic studies clearly show the benefits, a bigger benefit than you actually see in the trauma study. So the fibrinolytic pathways are activated very differently in those patients. I think if

you're going to try to stop hemorrhagic bleeding, hemorrhagic bleeding from trauma, that the model is there. There are thousands of patients, they come in 24/7, they're all around us all the time.

You know, it's a little bit of a sidebar, but I've done lots of rat and mice. Rats, pigs, rabbits. Those studies have -- and the *n* is very small, and you go take call, and in one night you take care of more bleeding patients than you did in the previous month doing pigs. There are a lot of bleeding trauma patients. And so why not study that model rather than a contrived other model that is less realistic?

DR. KING: Howard, can I just join in --

DR. CHAMPION: Yes.

DR. KING: I know we're going to have a whole session on animal models tomorrow or -- tonight or tomorrow? I just want to put an exclamation point on this issue that John brought up. You can go to the animal lab and pick whatever animal and whatever model. The group is very homogenous. And as soon as you take that data, just like the cardiac surgery patients and just like the orthopedic surgery hip fracture patients, those groups are relatively very homogenous, and those are more akin to animal models of hemorrhage than they are trauma. You take the average group of trauma patients, and they are very inhomogeneous, right? They don't all start with a blood pressure of 120/80, they don't all start with 30% blood loss replaced by 1 cc per kilo of crystalloid or -- it's very difficult to take anything

we learn in the animals and dictate how and predict how it's going to work in the very inhomogeneous human trauma population.

So I agree with John. You need to start with animal models, but at the end of the day we need to be looking at all of this in our enormous population of trauma patients. And that gets back to the issue of having postmarket data. We need to be able to look back and say, look, yes, it worked great in the animal lab, but not so much in our trauma patients; we need to keep this and get rid of that and so on.

DR. CHAMPION: We will be dwelling on the premarket versus postmarket, or that discussion, in just a moment. But before we leave this data acquisition in these patients, I'd like to hear from Rick Alcorta there, because data acquisition and studies in the prehospital environment are going to be critical to this. Sixty-four percent of civilian trauma patients die prehospital, and it's much higher than that in the military setting.

So John, I think, has established some format by which prehospital data could be acquired, but it is a non-trivial task to get representative samples of this patient population, which, by definition, are dying suddenly at the same time. You don't have time to introduce yourself and go through the niceties, and getting decent data in these settings, which is critical to understanding the scope and nature of the problem, is a challenge.

So, Rick, can you elaborate a little on that aspect of things?

DR. ALCORTA: Certainly. I'd be happy to address that. First, before I address this specific question, I want to reference some research that has been done, and that is the TIIDE project, Terrorism Injuries Information, Dissemination and Exchange. To me, that is the bridging of military experience with civilian experience. That's a step in the right direction, and it's been only really going on since about 2005 -- multi-collaborative process.

When we look at EMS data, really, it's in the last eight years that we've had the National EMS Information System, which is a standardized database that's nationally being recognized. And even as we speak today, not all states have implemented it. The reality is it's a standard set of definitions and it's a standard reporting process that we then collect very much like the national trauma registry, data-based registries that are being submitted by our trauma centers.

We have a challenge and an opportunity to, one, standardize all of our states to that data system for EMS, the NEMSIS system, realize it's in Version 2.2.1 and it's going to 3.3.4. And part of that is because it's going to be HL7 interfaced, so we'll have similarities between hospital data and EMS data, which we never had before. It's going to be a couple years in the coming, okay? And, two, we have an opportunity to establish things that are essential to document in the prehospital arena. The biggest complication I think we run into today is that somebody will put "tourniquet applied." Great. Where? What was going on? How long was it on? That data is not

being actively collected in an EMS record in many respects.

Too, it doesn't necessarily hand off an interface with hospital-based records. Those linkages need to occur. I've been in EMS for almost 28 years, almost 30 years and in a leadership position, and it's taken me 20 years to get the entire state on an electronic EMS database, and I'm still one county short, all right? The reality is that we have to keep pushing for quality prehospital data because that's where these people are dying. And until we have data of what they did, how they did it, and how they responded to that intervention, we aren't going to know, for EMS medical directors, trauma specialty services, is the device the right tool?

Is the intervention, the injectable, the fluid, whatever is used to resuscitate this individual, doing what it's proclaimed to do in either the animal model or in the laboratory model? Because we have to have those resources. And this is an opportunity to make that a real reality. We can link those datasets with the right set of questions, and there should be a formalized FDA reporting process that comes out of EMS data from each state, as well as from the trauma registries.

DR. CHAMPION: There's a whole panel on data, and I don't want to use up that role of this group here, but the elephant in the room, in many respects, is the cost and time to get the necessary data.

Colonel Rasmussen.

DR. RASMUSSEN: I have a couple of questions and follow under

Rick's comments. I actually changed the topic of my title, or the title of my presentation in the data session, to "The Right Data," so not necessarily more data, but the right data. And I don't want to take too much time on this, but the military really didn't make a turn in understanding prehospital death until, one, it looked at prehospital data, but then coroner data, medical examiner data.

And do you think that there's a role -- my first question is that -- to link in coroner data? Because really, to uncover or to shine a light on the hidden burden of mortality from trauma, again, if we're just looking at patients who make it into the ambulance and into our trauma rooms, aren't we missing the large burden of death from trauma in our country, is one question.

And then I didn't want to let John off the hook. I think I saw slides on some of the PROPPR data, maybe, that's coming out. And I have a question for John and then maybe the FDA hosts about how we reconcile studying devices that are really -- their effectiveness is going to be in the first 30 to 90 minutes. How do we set accurate endpoints and get rid of 30-day -- 24-day, 30-day mortality? They either stop hemorrhage or they don't, and it's really not that relevant whether or not a patient has a 30-day survival.

Two separate questions, and I know we'll talk about them over the next several hours, but one was coroners data and then two for the panel about setting appropriate endpoints for devices that are going to work or not

in 30 minutes.

Thank you.

DR. ALCORTA: May I address that?

DR. CHAMPION: Sure.

DR. ALCORTA: From a Maryland perspective, if you've seen one EMS system, you've seen one EMS system. The reality is, we try very closely to work with our jurisdictional medical directors who do quality review on challenging cases. And we connect them with the mortician -- or sorry, the coroner, medical examiner who actually performs the autopsies so that they can get some specific answers, usually when they are questioning care, not necessarily whether the intervention was successful.

A different shift: We're trying to make sure they didn't do harm when in reality we should also be assessing -- which we don't do well -- whether they did good even though the patient died. The other aspect is, our trauma centers get autopsy reports to look very much at that issue, both from a resuscitative perspective and a surgical intervention perspective. It's essential.

DR. CHAMPION: I'd like to hear from the FDA with respect to the endpoints, because we've had many discussions about 30-day and the relevance of it. And I think John has made the point very eloquently that we need to know early stuff. So does anybody in the FDA want to talk about approximate endpoints that are relevant to hemorrhage?

DR. CAVANAUGH: So just speaking mainly for the devices that the Division of Cardiovascular Devices reviews that are intended to provide hemostasis, I think, in many cases, the effectiveness has been determined by short-term endpoints, at least primary endpoints, looking at specifically time to hemostasis or other kinds of bleeding complications.

I think there have been other safety analyses that have gone out longer, but depending on the particular technology and the use, those may or may not have been actual primary analyses that were holding up approval or anything like that. I think, as in most cases, we're willing to hear what actually makes the most sense from a clinical meaningfulness perspective with regards to what these endpoints are. I think the precedence for relatively early time points has been established in some cases.

DR. KING: Can I just echo something that Colonel Rasmussen said? It passed his lips, and no one even questioned it, and I actually think it's a very important point. He said that it doesn't matter what the 30-day endpoint is, doesn't matter if they lived or died. And on the surface, you would say, well, that's absurd, of course it matters. And I want to support him in that comment because just like the waves of death from ARDS in the '80s, this is almost nonexistent now.

And the way this links in with his point is that if you can take a casualty who was bleeding to death, provide them an intervention that makes them not bleed to death, and then they survive to die from something else

later on, that's another hurdle altogether. So, if you just looked at hemostatic intervention and 30-day death, you may conclude that that hemostatic intervention is useless because they died a month later, when, in fact, the hemostatic intervention may be perfect and they're dying from something else entirely unrelated, reperfusion injury. Let us tackle that later, just the way we tackled the ARDS. So that's a long way of saying you're right.

DR. CHAMPION: Thank you kindly.

DR. MORALES: Hi.

DR. CHAMPION: Yes, sir.

DR. MORALES: Pablo Morales from FDA. I am a medical officer in the Division of Cardiovascular Devices, and I want to compliment Dr. Cavanaugh's comment. I think it is clear that this patient population, we won't be looking at a 30-day endpoint. I think you have enough data already collected in the military data -- that we know that we're talking about critical, perhaps, hours. And you know that around 60 or 80%, depending on the population that you're looking at, are going to die.

So I think it is fair to say that if you already have that knowledge, you can come to us and say that we want to look, for example, a patient dead or alive at 24 hours. They then managed to save his life. And I think we are conscious that the limitation of if someone die of something else, it doesn't have to go against a given device or a given drug or a given biologic. I think there are mathematical ways to tease out all these

confounding factors, but I think that the bottom line is you want to save a life and you save a life in not hours, but have minutes. So I think that that would be a type of data that we will be looking at to assess the duration of these new products for the patient population.

DR. CHAMPION: Thank you.

Grant.

DR. BOCHICCHIO: Thank you, Howard. Grant Bochicchio from Washington University.

One question that I have for the FDA, really, is how do we bridge the confusion? We're looking at endpoints, but we're still faced with differences between CBER and CDRH not still even having definitions of what is severe bleeding or more than moderate bleeding. It's now more than severe. I've been on discussions where there are disagreements on phone conversations about how you define it. And the regulatory pathway is extremely confusing. So, if you use the compressible world where there's a variety of products out there, the regulatory pathways and the definitions are different for the same exact indication.

Now we're going to the noncompressibles, and we still haven't answered the question on the compressible side, but if you have thrombin and fibrinogen in a product, your regulatory pathway is a lot different than if you have a cyanoacrylate in there because it's not a hemostatic product. Same exact indication, different pathway, different definitions. And as a

researcher in basic science -- and John's been doing this for years and a variety of people in this room that know exactly what I'm saying is, you really don't know what you're doing because you do these animal studies, you plan the clinical trials, the FDA changes their mind half the time, and we're trying to reach these endpoints we're all discussing here. You know, Dr. King and all these experts here are talking about trying to save lives, but we still don't even have the definitions yet.

So I was wondering if the FDA could provide us, is there a plan for CBER and CDRH to eventually get together and say, okay, this is what a definition is, this is how we're going to go about this, so that us and the academic community have an idea, how do we make that target if we're going to get a product that looks great, to test it the right way so we're not spending 5 or 10 years still trying to figure out what severe bleeding is to get that indication, to use it in theater, because these --

DR. CHAMPION: Grant, we're short of time. We got it. Okay, can someone here answer the question for the FDA, please?

DR. CAVANAUGH: Well, I mean, I think that was one of the things that this workshop is intended to be, a first step towards recognizing what the issues are, and then as next steps, in other settings, to work on ways where we can better develop our products and have consistency where possible. I can say it's different, from my experience, that people actually hang on FDA's definitions of things, in many cases. For the more

cardiovascular procedural-related products I deal with, there isn't as widespread awareness of how FDA defines things or what's in labeling, et cetera. And so it's in some ways comforting to know that this is actually meaningful here, and that's why, one of the reasons why I said before, we really want to know what are the meaningful things, from an FDA decisional perspective, to the other stakeholders out there. And so we look forward to hearing more about that during the workshop.

DR. ASHAR: Yeah. And if I can add to that comment. This is Binita Ashar, FDA.

We are your FDA. This is your government, you know. It's not that FDA knows best and we're telling you what to do. We want to serve you and get products out there on the market that help patients. And if you have rational thoughts about how we should create a nomenclature that would be usable for clinicians, academicians, industry, that would help inform our regulatory process, I think that that would be a great output for this meeting. So that's just one point I want to bring to your attention, that this workshop is a workshop. We are working to try to get some answers and chart a path forward.

The reason I'm up here is I actually wanted to thank you all for your talks, and I wanted to appreciate Dr. Holcomb's slide where he demonstrated that it's really the first hour that we're focusing on, and Dr. King mentioning the difficulty in assessing these patients because of their

variable nature, and Dr. Alcorta mentioning that it's very difficult. You know, we need some EMS guidelines on how we take care of these patients at the very early time point.

And so I guess my question for the three of you is, FDA often worries about how we take the clinical study data that we are basing our benefit/risk assessment on and translate that to the real-world environment, whether it be in the civilian population or in the military population. So I'm wondering if you have any suggestions about how that transition could more smoothly occur, whether it's in collaboration with some of the organizations you mentioned, Dr. Alcorta, or if we should be thinking about something in addition to postmarket requirements?

Thank you.

DR. CHAMPION: If you could be terse, please.

DR. ALCORTA: I will be quick. One, the NEMSIS project, Clay Mann is the point of contact I would recommend you get in touch with. The measures that you find in your Class II/Class III and potentially de novo postmarket evaluations, I think if you have a standardized set of criteria, I think that's where you should build it. Let me give you an example: EMS is very diligent about documentation of airway. Why? Because we realize you don't have an airway, you have a dead patient; and therefore EMS has to be proficient at airway management, so we're all about what device was used, what were the indications for use, what were the complications associated

with it, and what were the successful measurements to document adequate airway management and ventilation.

Build those same types of key components for any device you're going to put out that you have any hesitancy about and/or you want to have continued data. I'd love to see that for all of the hemostatic agents, and why? Because there's such a spectrum of them. I, as an EMS medical director, am challenged constantly because when I look at the journals, I'm reading vendor-based advertisements. I am not reading clinical evidence necessarily. Sometimes it's both. But you have to read every one of them.

Versus a set of tools that come to you, as an outside observer, who has approved this and would (a) get early notification of an untoward event; (2) be able to recall any of those particular devices or medications that are inappropriate; and (3) it would help the EMS medical directors make a good decision.

DR. CHAMPION: Thank you, Rick.

John.

DR. HOLCOMB: So I think your question is exactly the same as Grant's, actually. And I would say, just fall back to how we teach our residents, you know, which we do all day long. And I'll use a caveat from this week where we had a patient come into our trauma center, we had very good results at the national level of risk adjusted, and we had a patient bleed to death in our hands because he was unrecognized. He faked us out. He

looked good and wasn't. So, if the patient comes in with a hole in the abdomen and the pressure is 60 and the heart rate is 140, that's easy. There's no question about that. The scale is easy to construct.

Unfortunately, a lot of patients come in with a pressure of 100 with a pulse of 110, and they're not confused or disoriented, but they still have a lot of blood in their abdomen and need to go to the OR, and those patients are at 30% mortality. So the reason there's not a good scale is it's hard to do. And so for the FDA, I would say what we teach our residents is to over-triage versus under-triage. I think it's a critical concept in trauma, starting prehospital and in the hospital. I'd rather go to the operating room and do a non-therapeutic laparotomy and a patient didn't need it -- and you can't do it all the time -- than have a patient bleed to death in a hospital, right? So over-triage.

So we're going to use these devices on people who don't need them, in hindsight. But in the ED, in the first 5 minutes, there is no test that allows me to tell, conclusively, at the 95% level, what the intravascular volume deficit is. It doesn't exist. Maybe it will some day. And so you go to the operating room, make a hole, take a look, you know. Most of the times we're right, sometimes we're wrong. That's where the conundrum lies, and I think the FDA and the clinicians can come together with the under the over-triage rubric of risk and benefit and come up with some guidelines that we can all utilize.

DR. CHAMPION: All right. Thank you, John.

Todd, did you want to make a closing word here? Could you go to the microphone, please?

And also, while Todd's going there, I think we ought to be able to eliminate preventable deaths from isolated vascular injuries to the limbs, I mean, just as a proximate goal because nobody should bleed to death in civilian or military settings from an isolated limb injury. It's just not correct.

DR. RASMUSSEN: I'm not a formal debater, and I didn't take formal debate training, but --

DR. CHAMPION: At least not now.

DR. RASMUSSEN: -- I have a fair amount of experience around my house, and I know that to get the last comment in is good.

(Laughter.)

DR. RASMUSSEN: I've heard a couple -- similar to my house, things pass my lips without people hearing them.

So I said a couple of things, and I would challenge us to think about -- I've heard a couple of calls for categories and nomenclature. Please, I think, prove me wrong, that we should not use endovascular and exovascular. I mean, let's discuss that. They're different. They're hemostatic devices, but you can't -- one cannot compare an endovascular device and its properties to an exovascular one. They're different. And I would, as we talk over the next couple of hours and day, think about that. And there's not

many endovascular surgeons or interventionalists in the room, but this is a new era, and I think for those of us who have seen the management of coronary disease and vascular disease over the last 10 to 15 years, trauma is right behind. And if we start today by comparing a tourniquet to an endovascular balloon and evaluating them sort of the same in this trash bin of hemostatic devices, we'll be off target three to five years --

DR. CHAMPION: You know, we're going to have to have individual tactics and techniques. We're looking at all of these categories of adjuvant therapies for hemorrhage control.

Two things that I hope the next panel will take up, which we should have done here, one is should we be labeling drugs for combat use only or drugs and devices military use/combat use only? Is that something that needs to stay or should it go away?

And I would just like to thank everybody --

DR. KING: It should go away.

(Laughter.)

DR. KING: It's already gone.

DR. CHAMPION: I'd like to thank everybody on the panel for their contributions, and the audience for being attentive and questioning.

Thank you.

(Applause.)

(Off the record.)

(On the record.)

MS. KUMAR: Okay. Well, thank you. We're going to begin Session II. Session II is entitled Unmet Trauma Care Needs, and what we've done is we've laid the landscape in Session I. We've said what's out there, and we started to hint at what are some of the gaps that we need to fill. Session II is really going to take a much deeper dive, speaking with some of the trauma surgeons for civilian care, the military surgeons and healthcare providers, and then getting into the people that do the studies, the FDA perspectives, the user registries and epidemiology, and how we can look into some of those needs so we can fill these gaps.

I also wanted to introduce myself, I'm sorry. I had someone come up and request that I do that. My name is Allison Kumar. I am with the Emergency Preparedness and Medical Counter Measures program within the Center for Devices and Radiological Health. And it's nice to meet you all. I'm going to open up the session by introducing Dr. David Marcozzi.

DR. MARCOZZI: Good morning.

You know, this introductory slide, I almost want to rephrase a lot of my slide deck to say what they said, because I see a lot of similarities between the discussions that were had previously, either in the panel or in the PowerPoint presentations, and what I'm going to present here. I'm going to take the approach, though, slightly differently. Obviously, you can see from my titles, I have a couple different -- wear a couple different hats. I am

Joe ER, I work clinically and do that job. I also work from a policy standpoint on the preparedness side of the house and think about disasters.

And in addition to that, I have a military hat of which I'm going to be talking about today, my recent experiences overseas. I just came back as the prehospital medical director for the Joint Theater Trauma System, and I'm going to expound a little bit more about that. But a lot of the discussions, interestingly enough, have been on that prehospital piece, have been on the field care, so I'm going to talk about my experiences and at least some of the observations we've had to date in the JTTS world.

Obviously, the disclaimer. Any of my remarks are not by DoD, not by HHS, and not by George Washington University.

So you saw a great video by Lieutenant Colonel King. He mentioned and brought up the fact that when you provide care in the field, it is different than when you provide care in the field in the civilian sector or when you provide care in the emergency department or in the operating suite. And those top subtle differences make things change. Education change, what you carry on your back change, what you carry on your vehicle change.

Lance Corporal Bernard, September 4th, 2009, had a fatal event occur. Actually, Secretary Gates got wind of this picture. That is the lance corporal when an RPG struck his legs. He exsanguinated, and his last words were "I can't breathe, I can't breathe." So although we talk about, you

know, the granularity of this study is powered to this or this showed this, I need everyone to understand and appreciate that there are faces to the discussions that we're having here that are impacted, and there are still good guys fighting for good causes.

So I'm going to talk a little bit about JTS: what we know at least from my vantage point, what we don't know, and then how to engage further. And the truth is I'm a little humbled to be in the room and to be invited to talk, because it was in 1980, when we fielded the Dream Team for the Olympics, it was like Magic Johnson, Kareem Abdul-Jabbar, right, it was all those guys.

So you have Dr. Holcomb, Dr. Rasmussen, Dr. Champion. You not only have academicians, you have clinicians, you have operators. I don't know if you know this or not; Master Sergeant Costa is in the room. Master Sergeant Costa is a Green Beret, 18 Delta medic, multiple overseas tours. So not only do you have academicians and researchers, but you have guys who have done the job, who have taken care of him, in this room, to have this discussion. So here's my strategic pause.

Well done, FDA. Well done to have this discussion to bring folks into the room to fix this problem because it is overdue, it is time for impatience on this issue, and I'm glad to see everyone having discussions on how to save lives.

So, show of hands. They used to do this for Hurricane Katrina.

I use the same exact question I used to ask. How many folks know of the Joint Trauma System? Fifty percent of the room. Interestingly enough, DoD has a massive group and a massive warehouse of data. Echoed throughout a lot of the talks have been the fact that we need more data. Well, I will let you know the Joint Trauma System -- if you Google it, this is the webpage that comes up. The Joint Trauma System actually houses prehospital data, field en route care data, data from the medical treatment facilities. So we can actually start to get more granular, better understanding of when somebody gets hurt or injured, what the outcome is associated with that. So I will put a foot stop. If you take one thing away -- apparently only from a PowerPoint presentation, you only take about three things away. If this is one of them, I've won the war.

So we've made some progress. And it's interesting because you talk about progress and say, okay, well if you're at a football field and you've gone from your own 5 yard line to your own 10 yard line, you have made progress, young man. However, you still have 90 yards to go. There is a lot of work still to be done. 2011, we're working on data that we substantiated, and we have not affected care in the prehospital sector significantly at all. One out of four planes crash if you get injured in the prehospital sector. So, when I talk to medics on the ground, then I would say do you know why this matters? Do you know why this matters? Are you comfortable if one out of four planes crash? Twenty-five percent of the time, if you get injured in the

prehospital arena, you will die a preventable death or a survivable, potentially survivable death. Is that fine? Are folks in this room fine? Apparently not. FDA's not fine with it. They hosted this meeting.

But I think it's also important for us to champion this further than this room. We cannot palliate this anymore. So we've advanced. There has been some good work done. From the initial injury you look at now a system of care, just like EMS. The call comes in, prehospital care, what capability are we going to provide to that -- what en route care capability are we going to provide? Is it a medic, is it a flight nurse? Bring them back to a different echelon of care, a different hospital. In theater, they call them Roles 2 and 3. Basically, it's a different level of hospital, from -- similar to trauma centers.

Then you link that system approach, not just the widget, but a system-based approach to delivering care and linking that to outcomes. That's challenging work because that's not just I just put a tourniquet on, I have a 5% reduction in mortality -- that's system-based research. That's where I think that we need to push the envelope towards. Not just widget development, but system development. Providing the right capability based on risk, whether or not you're driving 50 or 75 miles an hour in Nevada or you're getting shot at in Afghanistan, a system-based approach to delivering better care.

So this is what we know. We're getting better at caring for

these types of injuries. And there is a host of literature out there around us, all of it quoted by the subject matter experts who, if they are the Dream Team, I don't even know if I'm the water guy. I may be carrying a towel or two or the duffel bag. But these are the folks who have done this research. It is time that this research now gets translated to effect care faster and better than we do currently.

You all noticed these were the slides that basically, the bottom line, the take-home point is lots of folks, lots of our military are dying in the prehospital sector, and the Joint Trauma System now collects data in the prehospital sector.

This was that summary. Look at, and foot stop, on the last bullet. If you want to take one thing away, look at this last bullet and let it resonate. The Tactical Combat Casualty Care guidelines that DoD promotes are not yet across all DoD. Master Sergeant Costa, in the back of the room, is very familiar with this. You know why? Because Master Sergeant Costa sits within USASOC, United States Army Special Operations Command. Where was this born? This was born in the special operations community. This has yet to be fully implemented across all of DoD. There's an educational piece to this. There's a technology piece to this. Not everyone has all of the pieces that they need to execute TCCC to save a life. And not only that, he mentioned evidence-based improvements around system optimization. Systems. Think about the system that delivers that care.

So this is what we know. We know pneumothorax, we know airway occlusion, we know hemorrhage is a problem. This is obviously borne out in multiple different pieces of literature. But let's talk about that control for one second, and I'm going to come to a next slide that I hope resonates with all of you, that Tactical Combat Care has not yet been fully implemented across DoD. And we need to develop the better widget, and your widget needs to plug into the system better than we do currently. So, when you think about developing your widget, and if those are out there in industry, think how it plugs into the system that gets adopted much more easily.

So hemorrhage control can be devices or therapies, and we talked about it in previous discussions. But not only do you stop the hemorrhage, but then how do you resuscitate appropriately? The fact that we are still working and noodling through FDP, freeze-dried plasma, the fact that we're still working through that, we need to rectify that problem. When you get shot, you need to have the ability not only in theater, not only if you're a special operations person, but if you're in any theater where you are at risk, you should not only receive blood products or red cells, you should receive plasma. There is a way to do it, we have the ability, we need to fast track that to get that to a solution. There also has to be, we realized -- and Colonel Gross out of JTS is a champion for the fact that we need the ability to provide whole blood. Whole blood resuscitates better than component therapy. TCCC guidelines just were revised to echo this. We

need the ability and a widget that allows us to provide transfusion, whole blood transfusion. We need to get there from here.

So let's talk about devices. Extremities, we do a pretty good job. We have tourniquets, and everyone's echoed that. Every soldier is kind of going in the theater, at least they were going into theater, all of them are going into theater without them. Now that we're scaling down, theater's changing. Evacuation times are changing. Remote care is actually becoming more of an issue, not less of an issue, as we draw down.

So, for junctional tourniquets -- Dr. Holcomb, you correct me when I'm wrong -- approximately 70% torso trauma, 20% junctional trauma, and around 10-13% extremity trauma for hemorrhage control, correct? All right, thank you. So about 20% we had the ability, look at the stats on how well we're doing that in theater. Seven percent. Based on wound mapping, based on who needed blood transfusions, actually received a junctional tourniquet. That's a problem. That's either the widget's not right, we haven't educated on it, they don't have the widget, but that's a problem.

So here are some additional gap areas. Keep forcing, keep pushing on PPE, personal protective equipment. Wherever you are, any soldier is going to appreciate it, the lighter, the cleaner, the faster, the easier it is to get on/get off, and the more protection it affords, the better we all are. We need systems-based research. We currently do here's this product, I'm going to research on this one, intervention, and then I'm going to have an

outcome, and that's easier, the systems-based research. But we need -- you are all the uber minds. How does a system affect care in approved outcomes?

Pain management. Currently right now we are still providing for potentially hypotensive patients or hypotensive patients. We are giving narcotics, narcotics that have the ability or have the potential to what? Drop blood pressure. TCCC guidelines now state ketamine. First line drug for pain control. But I will let you know that that is not the current practice in theater. So is it that we need a better widget, we need a better drug? Is that education? Is that all of it? I think that that's for all of us to digest.

Airway management. There is a champion for airway management at the Joint Trauma System. Lieutenant Colonel Bob Mabry, write it down. He is an outstanding guy to think about how to better manage airway. So, if you need hope or if you need engagement and you need thoughts about how to construct the better tool, that if you get a jaw injury and your airway is occluded and you have the guy who can take a knee next to you, your buddy, and provide you an airway so that you can then breathe, there's the widget.

Lastly, we talked about the fact that Dr. Holcomb was talking about, hey, you know, I had one guy, I wasn't sure he was sick; he faked us out, he got sick. That happens all the time. All the time. Not only in the military sector, but in the civilian sector. We need the better ability to assess

critical care patients, when they turn sour, when they don't.

So is it a new vital sign? Is it a new biomarker? Is it a device? Maybe it's all three, but uber minds come up with the answer. That will help us significantly. If you're in the back of an aircraft and somebody starts to go south and you know beforehand that they're going to go south and you start hanging blood products and you're able to save their life, that's where we need to be.

So my question to the room is where is my tricorder?

So let's be smarter faster. We need to be capability focused. Capability is the widget, is the education, and is the system that affects care. Data, data, data. We need our electronic health records to be able to link with providers and do an epi study so that not only are we doing one-off studies, we can do global studies for theaters in the civilian sector and particularly in the military sector.

Lastly, we do a poor job currently of utilizing "we." U.S. government, civilians do a poor job of utilizing the Joint Trauma System. I think we put them front and center, they become the center mass for training and for engaging FDA, engaging folks on how to better develop systems of care across both military and civilian sector. Operational and systems-based research. And FDA started with this workshop, but I think it's time to make that foundation and to make this concrete. And I think we do need to establish a joint DoD/FDA military use panel. The research gets done typically

in the special forces community; it then bubbles to the conventional forces and then bubbles over to the civilian sector. I think you could develop a joint approach between civilian and military that gets the best of the best of that.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Marcozzi.

I would like to, again, invite Dr. David King for his next presentation.

DR. KING: Good morning again. So this is going to be a fairly narrow scope here. There are a lot of unmet needs. My goal is to focus on the big ones, and I hope to make that clear.

I don't need to reemphasize, patients die before they get to the hospital, and they die because they're bleeding to death. And as we mentioned during the panel discussion that Colonel Rasmussen brought up, the goal is to get guys who would otherwise die to arrive alive at a surgeon and let us, the surgeons and critical care doctors, figure out how to solve their other organ problems as long as they're not dying from hemorrhage before we can even get our hands on them. Give us the chance to manage the complications. That should be our overarching goal in terms of this meeting and what we're trying to accomplish here and describing what the needs are.

So I used this slide in the previous deck for you to understand

the care continuum and where we need to focus; that is, the point of injury up until the point of initial surgical care.

So you don't get to put this very often. How often do you get to put a big check mark in the sort of problem solved box? It's pretty uncommon. Dr. Rasmussen pointed out that a decade ago we had, what, 9% of problem solved, and now we have almost 40% of problem solved. Well, between that 9 and 40 is this, right? We have really good solutions for extremity hemorrhage, and we have really good solutions for junctional hemorrhage. Now, those solutions may not be pushed out everywhere we want them yet, but they exist. So from a device/technology/development standpoint, I would argue the problem is solved; it's just a matter of pushing the technology out.

So as it relates to care under fire, there's not much -- I find it challenging to believe there's much else we can do to affect outcome during care under fire. However, there are a lot of things we can do during tactical field care and TACEVAC. So of all the things we can offer and all of the interventions we've been working on, what we still do not have is a solution for intracavitary hemorrhage control.

Now, don't be clouded by the issue. Resuscitation is not hemorrhage control. Resuscitation is a false bedfellow, right? The blood pressure is 60 and makes you feel uncomfortable. You give saltwater, you make it 90, and you say I feel better now. Probably you've done little to help

that casualty. Most likely you probably made them worse. Now, that's not to say patients don't need resuscitation; some do, the ones in extremis. But we need to get away from this idea that we need to improve vital signs to make ourselves feel better, which gets back to the second issue.

We need to have an intracavitary hemorrhage control solution, and we need to have a way to shuttle gas, right? So that means the current standard resuscitation fluids, Hextend, crystalloid, and so on, you don't carry gas. We need to deliver oxygen and we need to off-gas carbon dioxide and buffer acids and so on. And there's a variety of ways to do that, you know, freeze-dried plasma was mentioned, which is not gas carrying, but it addresses buffering and coagulation; pushing whole blood forward; packed cells. Packed cells don't work that well, whole blood, so either. I don't want to get bogged down in a single solution, but we do not have an answer for gas shuttling to replace critical hemorrhage losses.

So, for me, those are the two big existing gaps, the problems that need solving. We need a way to stop or slow ongoing blood loss at the point of injury up until that patient reaches a surgeon, such that they can live to reach the surgeon, and we need a way to replace critical blood loss with something that shuttles gas.

So, when we talk about novel hemorrhage control, novel intracavitary hemorrhage control, this is the problem. Try to understand this. This is not extremity hemorrhage. This is a trauma laparotomy, and you'll see

as soon as they enter the peritoneum here, this is not just a put a tourniquet on like shutting off the faucet. You don't know where the bleeding is coming from. The blood is coming up from all over the place. This is a difficult problem to solve. And you can understand why, for essentially the history of medicine, that issue has not been solved yet. We don't have a solution for intracavitary hemorrhage. And I would submit to you, part of the reason we're here is because there are some on the horizon, and this is a big deal for us.

Again, this slide reused to emphasize a point. That's me operating in some tent in Afghanistan. I don't need a lot of help, right? At this point of care, I have a lot -- it doesn't seem like you're in a tent in the desert or in the mountains. Doesn't seem like that's a lot of resources. That is an enormous amount of resources compared to the guy delivering care in that ditch that I showed earlier, right? That guy has almost -- that guy has resources that are on his back, and that's it. That's where the help needs to be. It doesn't need to be here in a tent.

So, if we look at what's available now for intracavitary hemorrhage control, there's a variety of things about them, they've already been mentioned. REBOA. I put the T-POD on because I think it's an under-appreciated, fairly important intervention for intracavitary hemorrhage that occurs in the pelvis, right, in the retroperitoneal space in the pelvis. TXA, we can debate about but arguably is an intracavitary blood loss amelioration

intervention. I don't know that I would call it a hemorrhage control intervention.

And then, of course, for sake of completeness, I understand this workshop is not about replacing losses, but this discussion of what the needs are or what the unmet needs are is not complete without talking about how to replace critical blood loss. That may be with packed cells, freeze-dried plasma, hemoglobin-based oxygen carriers, fluorocarbons, whatever. I don't know what form our gas shuttling critical blood loss replacement will eventually take, but we don't have the answer yet. And you can't have one without the other.

The battlefield design characteristics for our unmet needs are the same. And this cycles back to Dr. Champion's point about should we make a distinction? I would argue probably not because it doesn't matter how you start bleeding; once the bleeding is going, the populations become fairly similar.

And, again, I just want to use this slide to echo that same point. There are hemorrhage control interventions for the arms and legs and the groins. We have problem solved. We didn't have those in Boston. Our medical infrastructure was not carrying tourniquets during the Boston bombing; that's a problem for us. Furthermore, patients with intracavitary hemorrhage, no prehospital intervention, same as our guys in the battlefield who have no prehospital intervention. The difference here is that all of our

Boston bombing patients survived because they got to the hospital in 26 minutes, on average. The more critical ones were at the hospital in 6 or 7 minutes. This is not the case in the battlefield. We need a bridge, right? We need a big, giant hemostatic bridge. We want to take guys who are bleeding to death and make them arrive alive to a surgeon so we can deal with those problems. Right now, we have nothing to offer.

That's it.

(Applause.)

MS. KUMAR: Thank you, Dr. King.

I would now like to invite Dr. Anthony Pusateri, who is the manager of the DoD Hemorrhage and Resuscitation Research and Development Program, which is part of the Combat Casualty Care Research Program.

DR. PUSATERI: Thanks very much. It's a pleasure to be here this morning. I want to thank the organizers for putting it together, this together, and also for the invitation to speak. And good morning, ladies and gentlemen. I'd like to readdress many things that have been covered already today, but do it from a DoD R&D program perspective.

These are my opinions, not official statements of the U.S. government. And I want to hit three topics that I think are relevant. First is an overview of the hemorrhage resuscitation program and focus on the importance of hemorrhage, which we've covered extensively already. And

then let you know some of the results from a joint hemostatics working group where we produce prioritized capability gaps. And those gaps guide our R&D programs. And then a little bit, which I think will be relevant for later discussion about our use of and need for and use of clinical data.

This summarizes the Eastridge et al. paper. It's causes of death on the battlefield. We've discussed this several times today. Critical points are shown at the top, the "died of wounds" occurs after reaching a surgeon; "killed in action" is before. The causes of death in the battlefield are one of the key drivers of the overall DoD hemorrhage resuscitation program. The first step is our primary focus in the prehospital environment because that's where 9 out of 10 of the deaths occur. The next important point is that of the overall deaths from this study, 26% were potentially survivable. And Colonel Rasmussen mentioned this earlier.

When you take a look at the causes of those, 9 out of 10 of the potentially survivable deaths were due to bleeding. That is the real driver for the entire program. When you take a look a little further down, you can see that the breakdown is primarily truncal; there's also junctional/extremity hemorrhage, and this is from the period 2001-2011. During that time, the evacuation -- during that -- the median evacuation time, shown in the lower right-hand corner in the yellow, was 90 minutes decreased to 42 minutes later. We just heard that with the drawdown, they may be increasing now. I don't have any information on that. This is an important point because one

of our future challenges will involve much longer evacuation times.

The DoD's Hemorrhage and Resuscitation R&D Program includes all of DoD's efforts in the areas of stopping bleeding, fluid resuscitation, blood products for transfusion, and a path of physiologic response to traumatic hemorrhage. And we view this from basic and discovery research through clinical development. Our goal is to produce methods, drugs, and devices to stop bleeding and replace lost volume and mitigate the consequence of bleeding. We identified that there are up to 25% of casualties that could be saved if we could solve all of our problems in this area. And our focus of all of our research and development is directly linked to documented capability gaps. And that really highlights the importance of what I'll speak about a little later, and that is focusing capability gaps.

We have four strategic objectives. First, providing technologies to control bleeding in the prehospital environment. We clearly recognize this. It's a major driver for the program. We want to provide safer and more effective and logistically supportable blood products. Technologies and knowledge for improved damage control resuscitation. And, ultimately, next generation resuscitation for prolonged prehospital management and casualty survivability. The end state, which we hope to be able to reach between FY25 and 35, is that potentially survivable casualties will no longer be limited by technology shortfalls.

I'd like to change gears and talk about the results of a joint hemostatic working group that we held in January. The meeting was held in Fort Detrick the 8th and 9th of January. It was focusing specifically on externally applied hemostatic devices. We had 68 participants from all the services, the special operations, FDA, FBI, and others. It had experienced combat medics, surgeons, pathologists, a number of others were present. And then we also had 20 voting members at the end, which focused on delivering some of these objectives that are noted at the bottom which drive our programs. The one I want to focus on is identifying and prioritizing capability gaps related to hemorrhage control. And this was the follow-up to a meeting we had the year before.

Our approach was to look at the capability gaps by agreed anatomic regions. We reviewed available devices and also devices in our development pipeline. We had reports of capability gaps and problems with devices from experienced users from the field. There was an open discussion involving everybody, and then finally the final prioritizations were made in a closed voting session.

So first was the landscape of the available technologies and technologies in development. And you've seen this a number of times today. But just categorizing it. You see the broad capability is shown on the left column. Next are some specific technically identified capability gaps that come from a number of documents that we use. Role of Care 1 is

prehospital. Role of Care 2 is the first surgeon, if it's at a forward surgical team.

And then you can see a number of products that are listed. They've been mentioned before. All of these are in use by the military, or if they're already approved, they're in use, or otherwise we're developing them. So you see a number of topical dressings and tourniquets. The technology readiness level, if it's 9 it means it's FDA approved and fielded. And now we have FDA approval status. So we reviewed this for junctional bleeding, as mentioned. Four or five years ago we didn't have anything, but recently a number of products have become approved. So you see a number of devices approved there.

And then, finally, in controlling intracavitary noncompressible bleeding, there's nothing approved, but there are some expanding hemostatic foams in development, and there's the endovascular approach to hemostasis that's in development. So this was the landscape of what we had, and next what we did was to line that up against our anatomic capability gaps.

These are listed now as bleeding category. Those were the agreed anatomic subdivisions. We have subcategories and then rank: 1 is the most important, and then 5 will be still important but less urgent and requiring less resources. So, first, we broke down intracavitary into intrathoracic, intra-abdominal, pelvic, and intracranial. The gap is completely

unfilled. It accounts for the majority of hemorrhagic deaths. Now, there's hemostatic foam technology that's expected to be important in this area that's initially approaching abdominal hemorrhage. Endovascular hemostasis is also expected to be important in this area, initially focusing on intrathoracic and also abdominal. We also noted that selected junctional devices can also be used as pelvic binders, partially addressing that category of bleeding. There are no devices in development for intracranial bleeding. The panel believes this will likely take an IV drug or biologic approach that was not the focus of the meeting. Next is junctional bleeding: inguinal, axillary, and neck. And this is really a big success because as I alluded to, five years ago there was nothing in this category. We view this as technologically filled by four devices, but they have limited fielding. So this is pending DoD's evaluation, selection of devices we're going to use if we're going to select some over others, and then full fielding. And those are major steps. So we had active programs in those areas. Current approaches are external compression. We also noted that endovascular approach will likely be applied in this area in the future.

For limb bleeding, upper and lower extremity, we believe we have the 95% solution with currently fielded limb tourniquets. There are many tourniquets now available. Currently DoD is doing a review to ensure that we're getting the best value and have the best devices fielded, but still, we have the 95% solution. Now, we also identified an important future

capability gap will relate to battlefield scenarios with prolonged evacuation. And so we're going to need to understand the pathophysiology of prolonged tourniquet times and how to manage those for longer prehospital periods.

Another category that we addressed was deep wound tract, non- or partially compressible bleeding. The gap is theoretically technologically filled with the XStat technology, which has recently been approved. But it will still, at the time -- it's now approved, but at the time we had the conference, it was not yet approved. But it's still going to require additional tests and evaluation and fielding. And then there are other approaches also available.

And then for external compressible bleeding, meaning dressings, topical dressings, we also believe we have the 95% solution. One gap that we did identify, though, is that we will need a dressing that can function in the face of coagulopathy, and that can become more important when we have longer prehospital times.

There are a number of related areas related to the capability gaps we identified. As mentioned, hemostatic devices are part of a toolbox approach, a multi-factorial approach to prehospital treatment of casualties with traumatic hemorrhage. And any new technologies we apply and capabilities we develop can impact other procedures. So two specific areas the working group noted where aligned research should be focused in the future: First is the impact of prolonged use of devices, in the current and

future devices, for situations where we have evacuation of 12 to 72 hours. And I mentioned that earlier. This is a capability gap that is now emerging in future scenarios with initial entry operations, theaters that have extremely long distances involved; we could have much longer prehospital times. So we'll need to understand that pathophysiology and how these devices may or may not work.

We also need to optimize resuscitation approaches with each new technology that's developed. One specific example is how might endovascular balloon occlusive devices, REBOA, as discussed earlier, impact resuscitation? So we're going to need aligned research, more basic research, to understand those.

Now, a related topic, but stepping a little bit away, is DoD's use and need for clinical data, and I think there are some misconceptions. So I just want to point out, we see clinical data for all products for hemorrhage control and all products for combat casualty care. And we might get that data as part of an official FDA approval process, and if we do, that's -- I mean, that's great. It's certainly integrated with all of our needs. We may need additional data post-approval, maybe before full fielding. We may assess the feasibility under DoD relevant conditions. We might need some additional safety and efficacy under specific conditions that we believe are more relevant to DoD. And post-fielding, we certainly collect data for quality improvement, to continuously evaluate and update our clinical practice

guidelines and also to reassess these capability gaps to refocus and guide our future research efforts.

Some opportunities. And I believe there will be some more discussion on this later, but data on fielded devices through the Joint Theater Trauma Registry. We heard earlier that prehospital data collection is expanding. We can gain information from our allied military experience. But DoD does not conduct randomized trials in the theater.

We also sponsor and cosponsor civilian studies, single-center, multi-center, consortium-based studies. These can be prospective observational. They can be ancillary studies or add-on studies to perhaps a study that's sponsored by another agency where we're asking an additional question. Of course, prospective randomized trials, we don't have any right now for hemostatic devices, but we do have some for plasma, for example. And we would benefit greatly from a database to report and accumulate civilian uses of all of these new devices. That is to be developed, and I know there are efforts under way.

We also emphasize interagency cooperation. So, for example, we have pretty extensive cooperation now with BARDA, NHLBI, expanding cooperation with FDA and others.

So, to bring all this together, noncompressible intracavitary bleeding is the top priority, as you've heard. We are focused on the prehospital hemorrhage control as our primary effort. Future scenarios

involving prolonged evacuation times will likely increase the need for prehospital hemorrhage control and also introduce new requirements for prolonged use. I haven't specifically stated this, but FDA approval is required for all of our devices, and we seek clinical data from a number of different approaches.

Thanks for your attention.

(Applause.)

MS. KUMAR: Thank you, Dr. Pusateri.

What I'm going to try to do is save a little bit of time right before lunch to have some questions for these particular panel members, even though I know there isn't a panel session scheduled until after lunch for these speakers. So, if you have questions, please take note of them.

The next speaker I would like to invite up to the podium is Dr. Tim Emhoff. Dr. Emhoff is the Chief of Trauma Surgery at UMass Memorial at Boston.

DR. EMHOFF: Good morning. Again, I'd like to congratulate or thank the FDA for having this because I think this is a really important topic. And I'm going to spend some time in maybe looking at the gaps that are going to maybe fill the gaps. How many people here involved in EMS? Any prehospital people here? This whole issue is probably going to reopen this whole paradigm of scoop and run, stay and play. But what we're talking about here is not staying and playing; we're talking about staying and working

because we're bringing some technologies to the field. And I'm going to be addressing the unmet civilian needs. But we're talking about doing things in the field that may actually do some harm here. So how to get that done, how to get training in our EMS people, how to keep that training at a high level so that harm is not being done. How do you designate these devices for use and how do you triage these people which are -- and you're talking about doing this in a few seconds. It's going to be really, really difficult.

Someone brought up earlier, do we need to be labeling these devices or should we be thinking about labeling things for military use only? And I would be first to say absolutely not. I don't see much difference between someone who is blown up with an IED or someone in his truck blown up by his propane tanks filling up someone's swimming pool heater. I mean, that's what we see. You know, we see -- and, again, it doesn't happen very often, and that's probably one of the big problems when you're talking about this particular problem.

It doesn't happen that often that we're faced with junctional bleeding or intracavitary bleeding where the patient is just on his last extreme, it's his last breath. Yes, it does, and we've got to be ready to take care of that. That's why we have in-house call, we have in-house operating rooms available 24/7. That's why we have Level 1 trauma centers. But when you're talking about educating an EMS force and taking care of these and being ready for that unusual case, it's a different issue.

So we're going to talk about making the most of that golden hour. And when I teach ATLS, Advanced Trauma Life Support, we're dealing with that first golden hour, the early deaths, when they reach the hospital. What we're talking about here in this conference is what about these people that die before we ever see them? And I'd be remiss not to mention this biggest group of people because what that really talks about is what this really indicates. And we know the answer to this problem, and that's injury prevention.

And we can't go away thinking that we got the answer to everybody's bleeding problem, you know, once it's happened. You know, we got to stop these things from happening. This is a series of 753 consecutive patients -- this is San Antonio, Texas -- and about deaths, their mortality, and what killed them.

And what they found when they did this -- I suspect they were looking for the magic bullet in the trauma room that was going to save them, but really what they found was you save the most people by changing behavior and prevention. And I'm sorry, but that's -- you know, it's not very glamorous, and there certainly is not a whole lot of money being applied to this kind of research, but that's the bottom line. If you looked at those people that actually made it to the trauma center and then died thereafter, if you eliminated sepsis, if you had a magic bullet for multi-system organ failure, if you prevented every pulmonary embolism, and you had a perfect

system in all that, maybe you could reduce trauma mortality by 13%. You know, not much bang for the buck there.

So where is your bang if the bang is prevention and protection?

Another study, this is from Miami, essentially the same thing. This gets a little bit at one of the issues that we're going to be talking about here. Here's 556 deaths, it's over five or six years, in the first hour. Median time to arrival, 39 minutes; blunt and penetrating. Most common cause of death: CNS. And other speakers also said this, also. Now, they're possibly preventable, though. There were 35 patients that had a single organ or a single vessel injury that died. And this is where all this occurred. And is this where we're really talking about noncompressible hemorrhage? Why did they die after reaching the trauma center?

And the other sobering thing was that most of these, they're going to die, they die very early, as other people have said. And you have very little time, you have a few minutes to really intervene here before the patient is un-survivable. The time now includes scene time. So we're talking about having a workforce of EMS and physicians in trauma centers that essentially got to work together here, and they got to be doing the same thing. We're talking about medical control and training that's got to occur because that time being used at the scene, like I said, it's not staying and playing; it's staying and working, if we're going to talk about intracavitary or junctional or noncompressible hemorrhage.

When I looked at my own experience, I looked at two years. This is our 2011 experience. We had 85 deaths in our trauma center. We mainly see blunt trauma, have about 3,000 activations a year. It's a very small percentage of the actual number of people that walk through our doors, which is like 120,000 a year. So I've got to keep a cadre of people that are ready and willing and able and train, you know, to take care of these sometimes very seriously injured patients.

There were 85 deaths, 78 blunt, 8 penetrating, and there were 15, what I would call, immediate deaths, people that reached our door that died someplace else before they actually got care in our ICU. Some of these went to the OR in angiography, some of them were DOAs that sort of were maybe alive but we really couldn't tell, so we did things to them, you know, trying to save their lives, and there were very few that had died from ongoing irreversible hemorrhage.

When I looked at where they came from, there's all series of reasons: They fall, the motorcycle crashes, pedestrians, stab and gunshot wound, motor vehicle crashes. And I looked at the possibly preventable. There were some that, for ongoing hemorrhage both in the chest, post-cardiac arrest, either from hemorrhage or from anoxica injury or multiple sites. So 11 of these possibly preventable or reversible, and this is in one year's time.

We looked at our experience a little bit differently, 2013; 107

deaths. Brain injury was primarily the problem for early deaths; 58% of these people that died early on or that died in our trauma center died from brain injury. Pulmonary, which is inflammatory reactions of sepsis and pneumonia, another 19. Bleeding, now 6%, five of them in the chest, one in the abdomen. And then I looked back and look at -- there are 23 immediates or those people that came in and within a few minutes or hours died, although they reached our doorstep, we thought was being able to survive. There were some DOAs. Two died in the operating room, six from brain injuries that were immediate, and seven we thought that probably died in the prehospital scenario but had a capability, possibly, if using some extraordinary techniques, to try to resuscitate and reanimate. And these are the people that I'm going to talk about here in the next few minutes.

So the issues around when people die in trauma, when those early deaths -- there are issues on triage, airway control, hemorrhage, and initial resuscitation.

I'm going to focus now on -- because this is what this is about. It's control of hemorrhage, and not the easy hemorrhage, the extremity hemorrhage, the hemorrhage that has occurred but the patient is alive and well and off to the OR. This is noncompressible torso hemorrhage, so there are large intracavitary axial vessels; there are solid organ injuries, Grade 4 and 5 spleen, liver, kidney injuries, maybe combined; pulmonary parenchymal injuries; cardiac wounds; and complex pelvic fractures. These are things you

can't put your finger on, or putting your finger on takes a trip to the operating room and getting something in your hands or putting something in a vessel and trying to get control.

How do we do this? Well, you know, up to a few years ago, uncontrolled intra-abdominal hemorrhage that seemed to be temporarily tamponaded, what we did, we went into the left chest, we clamped the aorta and went off to the operating room and then opened the abdomen with aortic control. Now we can control the aorta very, very much more easily. In fact, this is now how ruptured aortic aneurysms are taken care of. They're not opened until the aorta is controlled with an endovascular device.

Well, this -- you know, in this series -- and we still do this occasionally, it's a relatively low survival, but this is 16% that wouldn't be alive probably if this wasn't used. But this is going into the chest, it's a major invasive procedure, high physiologic cost to do this, and this is just to get control of the aorta.

I'm surprised Dave didn't talk about this, but other ways of improving intracavitary bleeding is to inject something in that cavity, increase the pressure, stop the bleeding. This is an animal study that Dave and his partners did at Mass General. This is the closed abdomen in a swine model, injected polyurethane foam that expanded, increased intra-abdominal pressure, and temporarily stopped hemorrhage or slowed the hemorrhage down. What did this do? This didn't fix the problem. This gives you time. It

gives you time to get them to that surgeon who can now get his hand on that single vessel, that single organ, whatever that hole is and now, you know, to fix it. The thing you have to start to understand, though, about all of these -- and this has been alluded to -- animal trials or control trials, like they said, it's normal physiology and normal animals who aren't smoking and who aren't on anti-platelet drugs and are not taking anti-thrombin inhibitors, okay?

So this assumes a free open peritoneal cavity and the patient hasn't had three bouts of diverticulitis and his abdominal uric aneurysm operated on 20 years ago, and that isn't always the case when we try to translate this material that we're seeing in young, healthy combatants to the population that we're seeing in our trauma centers now, which is, I can tell you, rapidly, rapidly aging. It is not unusual now to get an activation of that 100-year-old fell down stairs, okay. It happens, and it's happening more and more, and that physiology and that patient has nothing to do with that 23-year-old who was shot.

We also heard a little bit about REBOA or the occlusion of the abdominal aorta through catheter techniques. This is something that was done way back, as early as the Korean War, and it's coming back, and it's coming back with a vengeance, and it's an amazing technology. Some of it needs some fancy equipment. There are devices now that can be placed blindly and without fluoroscopy, so we're talking about maybe something that could actually be applied in the field, and there are some places that are

actually doing this to try to control the intra-abdominal aorta with an occluding balloon.

This is a set of studies that used this device, one of them from Shock Trauma. The second one was a fluoroscopy-free device. And also the third one shows that the physiologic tolerance of this is much, much better than trying to open the intrathoracic cavity and clamping the aorta. It was just funny or interesting, this first report, report is six patients. If we recall the first studies of intra-abdominal hypertension and abdominal compartment syndrome, it needed three institutions each supplying cases over a period of years to actually report on this, and here are two or three institutions reporting then their two or three cases. Two deaths out of this group and two of these -- and both of them cerebral.

And this goes, I guess, also, to the issues that we heard earlier that when we're talking about hemorrhage control, it's hemorrhage control in the first few minutes or hours, that we shouldn't be talking about 20-day, 30-day, 60-day mortality because then the issues are absolutely different. And I would second that, that we've got to be talking about what are these good for and what kinds of timeframes are we talking about?

So REBOA: Occluding the aorta. The last thing I'm going to talk about is, you know, we're going to cause some problems here. And, again, the organs are at risk. Just because you occlude a blood vessel doesn't mean you're done. The clock is ticking. You clamp the aorta, you blow that balloon

up, and the clock is ticking. You've got 30 minutes of warm ischemic time before those intra-abdominal organs don't -- start dying and you have less time than that, that brain and that heart are going to be irreversibly injured.

So the assumption is when you use these devices, you've got some kind of perfusing rhythm, you have a secured airway, you have massive transfusion that's going to be available to you when you're done doing this, and you have some non-exsanguinated hemorrhage. So someone has exsanguinated to the point where he's got some perfusion going on and now you're trying to control it, okay?

And this is not the case, necessarily, when they bring that patient in who is DOA, who just took his last heartbeat about 30 seconds reaching your door. Now, what's propped up to take care of these -- these so-called hybrid rooms. And this is the hybrid room that we have at UMass. This allows the use of these endovascular techniques while also allowing you intracavitary exploration, done both at the same time.

I would say that, you know, we need to be documenting the use of these rooms, what's going on in these rooms, what kinds of success rates are you having in these rooms, and what's working and what's not. So here, I think, is a perfect opportunity for some kind of database, some kind of reporting mechanism, because this is being done. It is being done now for truncal hemorrhage, truncal injuries by our vascular surgeons in conjunction with our trauma services, you know, to get control of intracavitary vessels.

The last thing you've got to think about is organ preservation, okay? When you're talking about non-perfused rhythms, you know, the paradigm of resuscitate, fix it, and then get the patient well in the ICU, that has to change because some of these people come in with non-perfusing rhythms or they come in with exsanguinated, truly exsanguinated hemorrhage. You've got to find the injury first, fix it, and then reanimate that patient. And what you give them to resuscitate, what you give them in the prehospital scene to protect their organs is a very, very important issue. Where is this being done? Well, this kind of research is being done daily in our ICUs, trying to protect organs for organ donation.

So this is another great opportunity for research. How do we maximize organ procurement in someone who is brain dead, or how do we maximize organ procurement in someone who is not brain dead but who is going to be a deceased cardiac death donor? These kinds of organ preservation techniques are being studied, and this would apply here when we're talking about how to maximize that time for patient salvageability.

So, when we talk about exsanguinated hemorrhage, this is a non-perfusing rhythm, patient's on complete arrest with, say, proximal aortic wounds, cardiac wounds, pulmonary hilar injuries. Balloons and intracavitary devices don't work here. You've got to repair before reperfusion. So the devices don't work, you've now got to go in and fix this, and now you've got to be thinking about how am I preserving organ function.

So this is my view of where the opportunities exist for unmet civilian needs. For exsanguinated hemorrhage research opportunities, number one is access and triage. How do we triage these people very, very early in the scene? What do we give our EMS people in terms of TXA, prothrombin complexes, lyophilized fresh frozen plasma, packed blood cells? What do we give them in their armamentarium to try to get that patient viable, with viable organs, you know, back to the trauma center? Do we cool these people, how do we do that? What about cold or oxygenated perfusates? Portable pumps. There are such things, battery powered perfusable pumps we can actually apply to perfuse these organs, to preserve their viability while they're getting to the trauma center.

And what about their re-warming, when do we do it, how quickly? With what? Do we perfuse and do we use other organ preservation fluids? What about reanimation, protecting the cerebral cortex? You know, the animal that survives 30 minutes of cardiac arrest is not the same as a 23-year-old or a 70-year-old that survives a cardiac arrest. What we find almost invariably is that we can save all the other organs, but the patient wakes up with a dead brain and then we're talking about organ donation. So the cerebral cortex is a very, very -- it is the rate-limiting step here, and we've got to learn how to protect that better. So we've got to learn to preserve organs at risk, and again, these kinds of studies are being done in our transplant centers.

So, for noncompressible hemorrhage civilian unmet needs, there is process unmet needs: identification, maintenance of infrequently used skills. You know, these things don't happen that often in the civilian sector. How do we get these people trained and keep them trained? Where do we put them? Do we have reanimation centers of excellence like we do with Whipple procedures and these -- you know, some procedures that we don't have very many doing?

We also have device needs: endovascular catheters, cavitary access, how do we get access? Maintenance fluids. You know, crystalloid is the enemy now. When we know there's massive transfusion and patients are getting massive transfusions, the crystalloid comes down. And we've got to have better resuscitating fluids.

We need reliable vascular access. Do we use IO, arteriovenous access? How do we gain it? How do we get people in the field able to do this and with reliability? And also, you know, other devices to maintain perfusion while that patient is being transferred.

These are big, big issues. But let me just say, the last thing I will say, these are not something that you're going to solve over a year or two years, but if you are addressing this problem, okay, we're looking at database, how do we get information? What's working? What's not working? We are going to improve the overall prehospital care of all of our injured patients, not just five or six or seven or eight. At my hospital, they're going to come in

next year with some noncompressible hemorrhage. The care of all those people, the 3,000 activations we're going to see, is going to improve and we're going to benefit all of our trauma patients, not just the ones with this problem.

So this will lead to what I call ASP, allowing hypotension, hypoperfusion with some kind of injectable perfusate. It may be correcting coagulopathy in the field, may be cooling them, may be transporting them to that specialized center. And then ongoing hemorrhage control, externally/internally, identify those people that need repair. And then resuscitation and then lastly preserving viability post-reperfusion. Do we cool, do we re-warm them? Do we use cellular preservatives? Those are, I think, the biggest issues moving forward with this very, very injured group of people.

(Applause.)

MS. KUMAR: Thank you, Dr. Emhoff.

I would like to invite again Dr. Rick Alcorta to come and provide a few more details on the EMS unmet needs.

DR. ALCORTA: Greetings. Glad I'm back up here again. It's a delightful place to be. One thing that's very clear, both from my presentation and many of the ones you've heard today, we really are not vendor-specific or aligned with any of these products, et cetera, we're talking about. At least I am not. I think it's also very interesting that you're seeing people that have

not consulted previous to the conference having very, very similar views. You'll find that in my presentation I am literally reiterating many of what my predecessors in this presentation have actually focused in on.

And I'm going to really take the more narrow approach because the whole concept of resuscitation clearly covers these critical phases, but I'm going to stay in the Phase I, which is really bleeding control pre-definitive care, because that's the EMS domain.

And when we look at that capability, we really should have some ideal resuscitative fluid because we don't have one short of current circulating -- you know, patients' blood. That's the only thing we really have. We need something that maintains and augments coagulation factors, oxygen-carrying capacity, long shelf life, non-infectious/non-toxic side effects, and readily available at low cost. So it's ideal. We don't have it, but that doesn't mean we should not continue to strive for it.

And that becomes a critical component because the closest thing we currently have is the patient's own whole blood. And then we start looking at packed cells, fresh frozen plasma. As you've heard, crystalloids are no longer in vogue for tremendous amounts of volume resuscitation. There is Hetastarch, expanders, TXA, and the permissible hypotension that you heard from previously is basically a stopgap in an effort to not fluid challenge them, blow off clots and neutralize or dilute any coagulation factors that you may have, and it's really trying to buy you time. That assumes that you know that

this person isn't going to arrest before you get to the department and they have a surgical team waiting for you. Not every hospital is a surgical center.

Please, from a perspective, if you're not familiar with trauma systems, it's important to understand that local emergency departments with hospital surgical capability averages 3 to 5 hours to get an entire surgical team operational versus a trauma center that has -- as you've heard, 15 minutes is a good time to get a patient to an OR suite. And that's with everybody on standby in the facility ready to go. So, when you start talking about the permissive hypotension, you are spinning a roulette wheel because you've got to have that surgical ability to control or correct that problem.

We have swine modeling that's been demonstrated, that demonstrates at least a product that has some positives on the horizon, and that's part of what we're looking for. I'm looking for a product that EMS can carry, can put on our helicopters, put on our ambulances, have a relative long shelf life that can meet coagulation issues. And there are a couple articles. One was done talking about freeze-dried plasma in *J Trauma* in 2008, one of the earlier presentations.

And recently one that was a special paper done relative to the Israeli Defense Force, medical command structure, implementing it as part of their interventive process. Both of these are demonstrating that there is some potential here, benefit, to address one of those challenges that we have from a public safety/EMS response profile to try and correct a coagulopathy

that we don't have the ability to do today or an ongoing hemorrhage where those coagulation factors are being consumed, particularly the cavitary lesions, either intrathoracic or intra-abdominal or pelvis. Very critical components.

I want to then emphasize datasets. And to me, the second important piece, when we talk about unmet needs, is linking of existing datasets. And we've touched on that here, and we're going to touch on it really on the third presentation. But tied to the great job of stepping forward on this, they've looked at explosives, which is probably one of the leading uses by our terrorists to impart stress on the system and make us react. They've already got documented evidence that we've learned from blast injuries and blast lung, and it changes our practices and how we're assessing patients. Patients aren't necessarily being discharged when they don't look bad initially until their lungs start to fill up with fluid.

The next thing we need to do, again, is align our databases. The FDA Level II/Level III interventions, medications, procedures, et cetera, need to align with the NEMSIS dataset, which is the National EMS Information System, and which has become -- is being moved to the version 3.3.4 to have the Health Level 7 interface for hospitals and the ICD 10 codes and using the SNOMED diagnostic codes and categorizations. The National Trauma Database focuses on Injury Severity Scores, ICD 10-CMs, and surgical interventions. Again, we're getting closer to measuring apples and apples

and apples. I think that's very important.

When we look at airway management, the reality is this is a model that EMS has been doing for years, but it's very narrow. There are very few things that we do in a prospective way, making sure that it's a safe device to put on an ambulance. We've got some evidence that usually comes out of a hospital or an ED setting, and we translate it to EMS, not necessarily because it's been validated in that environment. So we do that, and then we find, oh, it works great. Well, I'd like to think it always works great, but not always. And that goes for Rapid Sequence Intubation and other resuscitative interventions that have a tendency to be a hot button. Why? Because we don't necessarily have good data from the EMS sector. Got to have those indications, the device, successful measures that we can do, measuring the complications as well, and then EMS and institutional review. Should we not have FDA also being able to see access to that information?

We want to integrate those in an organized way with a continuous injury and recovery model from the initial insult all the way through to rehab. I know this is kind of idealistic, but that's what we're being asked to address here: What are those unmet needs? And we should select certain priorities and interventions and medications that come from the FDA, saying this needs to be one of our benchmarks, not just pre-approval and authorization and say have a good day. It needs to then be one of those things that if it's going to be used, you meet these standards, period. And

that means EMS as well, so that we can then look at research platforms, et cetera, on an ongoing basis.

The ideal resuscitative fluid, to me, has not yet been discovered, but we're certainly working toward it. I think there are products that have an opportunity to be supportive. If you look at some of our technologies, when we look at our preventative measures in other arenas, by different organizations, we look at the biotechnical environment that we're worried about. Influenza virus coming out. We look at Ebola currently in Africa. There are triggers that make us very unsettled, and we set targeted grants for improving or developing either a cure, strategy, vaccine, et cetera. Why aren't we doing that to the ideal fluid? Why aren't we establishing grants that very clearly target that is the solution that we need to address? Because it has significant properties that are unique, but the opportunity is upon us to align both premarket, aftermarket, and continuous.

What we need to do is plan, do, and check. One of the things that we don't always do very well is check what we've implemented, and we rely on more surrogates or indirect answers than direct answers and then act. And that act may be to recall an item or to augment an item or use it continuously as the standard of care.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Alcorta.

I'd like to invite Dr. Jason Sperry up to give us a perspective on some of the prehospital studies that he's done. And Dr. Sperry is with the University of Pittsburgh Medical Center.

DR. SPERRY: Thanks very much. It's a privilege to be here. And I want to talk a little bit about a couple trials that I'm involved in and it may shed some light and touch some topics that have previously been touched upon already.

So, first, these two trials that I'm involved in are funded by the U.S. Department of Defense, an additional two others by the Prehospital Use of Plasma for Traumatic Hemorrhage program; and two other institutions, University of Colorado with the PI, Dr. Moore, and Virginia Commonwealth University, Dr. Bruce Spiess, are also involved and equally funded. These studies are also providing samples for the NHLBI Institute and TACTIC, which is another consortium, NHLBI and DoD collaboration, and we provide samples for those studies.

The topic is mostly going to be about emergency research. Because this is right before lunch, too, I'm going to be very expeditious and quick. But emergency research and typically in the prehospital setting has been done before. This program is not special regarding that. And the Resuscitations Outcome Consortium and Dr. Holcomb have done this emergency research, and it has special caveats and important types of hemorrhage control that we're going to talk about, but these people have

already done this, and we're following in their footsteps.

Real quick, now I'm going to talk a little bit about the PAMPer trial that I'm involved in. We're going to talk a little bit about pitfalls and some hurdles regarding IND application, IRB, and prehospital training. And then quickly touch on the STAAMP trial, and I'll fill you in a little on what these acronyms mean. And some lessons learned regarding this.

So this is what you've heard this morning. This is what we're trying to prevent. We have a very focused time point when we can potentially prevent this. And it may involve the prehospital setting, as you've already heard the importance of that regarding civilian injury.

Acute traumatic coagulopathy is something that -- patients have a tendency towards bleeding when they're severely injured, and if we can prevent this, this may allow the delay of hemorrhage to get to the surgical controlled bleeding. You got to get them to the operating room and maybe bring this to the prehospital setting, maybe affecting and reducing coagulopathy, which is a tendency towards bleeding, may allow that to occur. Obviously, prehospital setting is going to be where this may be most beneficial.

The earlier the better. We've talked about time is of the essence, and if you start bringing something that may have some benefit to the prehospital arena, whether it be plasma, tranexamic acid, or other things that can provide time and minimize bleeding, and this may improve outcomes

overall.

My institution at the University of Pittsburgh has a very busy air medical transport service, and it actually provides services across the state and Maryland, West Virginia, and Ohio. And so it's one of the busiest, and I utilize this resource for some of the research that I have received.

So prehospital plasma. We've talked about plasma as a resuscitation fluid. Giving it earlier may assist in preventing coagulopathy or the tendency towards bleeding. So why not bring the treatment to the patient? Considering the helicopter as a mobile blood bank, is it worth the resources? Universal donor. You can use universal donor AB plasma. And in this case, we were funded to look at thawed plasma. There are other forms of plasma that may be more beneficial and have longer time where they can be used, and thawed plasma has its specific properties, which we'll talk about.

So this is the PAMPer trial. Prehospital Air Medical -- PAMPer, they didn't have anything for the "e-r" -- trial. This was funded four years: the Department of Defense, Telemedicine and Advanced Technology Research Center, to Phase III, four-year, multi-center, prospective, randomized, open label -- because you can't prove it. You can't do blood transfusion in a non-open label trial. And interventional trial.

The study overview: To determine if prehospital air medical plasma improves outcomes as compared to standard air medical

resuscitation. Our primary outcomes were initially blood transfusion requirements and mortality in the first 24 hours, but as discussed, after required by some of the requirements for emergency research, we did have to exchange our primary outcome to 30-day mortality for giving two units of plasma in the prehospital setting. We're also looking at blood transfusion needs in the first 24 hours, multiple organ failure, acute lung injury, and coagulopathy.

We're using TEG and measuring some cytokines as some secondary outcomes in addition to clinical outcomes to randomize trial because of helicopters and plasma requirements and getting that plasma to the bases. We had to randomize it by month, so airbases, helicopters in a multi-center fashion are randomized to either be control for that month, which is standard care, or plasma for that month. This complicates a little bit of the power analysis, but we did it in a fashion that allows it to be appropriately powered.

Our inclusion criteria, which is important. Some of this was obtained from the ROC trials. And we looked at hypotension below 108 with tachycardia -- excuse me -- systolic blood pressure below 90 and a tachycardia $>$ 108 or a systolic blood pressure $<$ 70. And this has been shown to be associated with massive transfusion, the requirement of blood transfusion, and in general predicts a pretty severely injured trauma patient by these inclusion criteria.

We had standard exclusion criteria. If you were shot in the head or greater than 5 minutes of CPR or you're a known prisoner or pregnancy, extremes of age > 90 or < 18, and if you're wearing an opt-out bracelet because these -- you're going to hear in a little bit. This is waiver of consent research for emergency research, so the patients don't have the ability to opt out or consign consent, which is what's special about this type of research in the prehospital setting. The intervention is two units of AB thawed plasma. If it gets initiated in the helicopter, it's continued, you get the two full units. And that's the full intervention.

We also try to minimize crystalloid, as you've heard, because crystalloid is thought to dilute your coagulation proteins and may have its own inflammatory process, so we sort of built it in the prehospital setting to minimize crystalloid. If the patient is hypotensive, they can receive blood if they're carried on the helicopter or crystalloid bolus, but if they're normotensive, try to minimize crystalloid and just give maintenance crystalloid fluid in addition, following the plasma.

This is, again, a multi-center trial, six different centers representing Cleveland; University of Louisville; Vanderbilt, Nashville; Parkland, UT Southwestern; and University of Tennessee, Knoxville; in addition to Pittsburgh.

Power analysis. We were powered at 30-day mortality, which was more difficult, of course, and not the ultimate outcome because there

are a whole lot of things that occur between the first hour of injury and two units of plasma and 30-day mortality, which is -- but this was mandated in our IND, which I'll talk about in a little bit. We're powered to detect 14% difference, 22% versus 8% and two interim analyses. Two hundred and sixty-five patients were required in each arm out of 530 over four years of enrollment.

We started enrolling. It's been about two and a half years of stop signs and hurdles to overcome. We started enrolling beginning of this summer, and currently as of September 1st, we have six sites out of six sites enrolling. We've enrolled 21 patients at this point in time.

And I have a little bit of some preliminary data. This is just a TEG analysis of some of the patients that were in plasma and control from my own institution. And you may not be familiar with looking at TEGs. You'd like a nice, big, wide, almost like in a persistent wide TEG tracing. And as you can see, at least some of these don't have the full run, but you can see in this tracing, it starts to narrow. There might be a little bit of a lysis occurring, and again, there's no comparison here. This is just preliminary data. These are some of the controls that did not receive plasma. You can see it starts to narrow. There may be some lysis of the clot, and the clot isn't as stable. This is less thick clot strength and here is -- just importantly, as we have discussed traumatic brain injury. This patient died, had severe traumatic brain injury, and you can see by the TEG, relative to the other clot strength TEG readouts,

this patient had severe coagulopathy, and this may be induced somewhat by traumatic brain injury. Obviously, this trial isn't able to predict whether someone has traumatic brain injury or whether they're dying from noncompressible hemorrhage. We can't tell by those prehospital vital sign inclusion criteria, and this patient had a traumatic brain injury.

So, real quick, the main focus was to talk about possibly some pitfalls or some hurdles of this type of prehospital research. One is that this is all under the Code, Part 50 in §50.24, the exception for informed consent requirements for emergency research. That's sort of the first hurdle.

You need to get an investigational new drug application and get it approved for these types of research. Irrespective of the drug, plasma can be given, it's FDA approved and by the American Blood Bank Association, but you need to get your own IND to do this type of research, and there are a whole bunch of regulations. And obviously I hadn't done this before. When I applied for this IND, I actually got help from Dr. Holcomb, who had recently done it himself, and we arranged our protocol, we attempted to, but the goal is -- as advice and some of the hurdles -- that the protocol needs to meet these requirements. And because ours didn't, it took 12 months to get an IND. We had to answer 72 comments, made multiple meetings, and it required four full revisions. It was helpful to have a pre-IND meeting, which you discussed, some of the things in the process. We learned a lot, and it benefited us from other trials that we've done, but it did take a full year up

front. Probably could have minimized some of that time by doing it in a more smooth fashion.

So waiver of consent for emergency research. You also have to do community consultation, which is you notify the community that you're doing this study and that they have a chance to opt out, whether they wear a bracelet or there are different options. And you have to publicly disclose, before and after the study, to do this type of research.

I have the benefit at University of Pittsburgh, we have the Resuscitation Outcomes Consortium there, and they've done multiple prehospital waiver of consent trials, so it's well set up. And we were able to get our community consultation done in about 6 weeks, which is relatively efficient.

And that includes doing patient questionnaires in trauma clinics, bus advertising, random digit dialing for the communities that our helicopter bases serve, an NPR radio spot, newspaper ads, et cetera, et cetera. And I do have the benefit of having experience. Our institution has experience with this, and I collaborated with people that have experience and were able to get this done relatively quickly at our institution.

Other hurdles is that this was a multi-center trial. Most of the devices that may be talked about here in the next 2 days are likely going to require multi-institutional trials. For them, individual sites are going to have to get their own IRB. Every institution has their own IRB and their own

requirements for community consultation. And each has to be added individually to the IND approved by the FDA.

So you can see where time becomes -- trying to go through the FDA, the IRB, the community consultation, and DoD. It added about a little over two years to get this trial up and running.

Some other hurdles. Federalwide assurance. Because these prehospital organizations require, need to be covered under an IRB, and FWA is really the agreement that an IRB is covering these prehospital organizations, whether it be an ambulance for prehospital, you know, an ambulance system, or a helicopter system. And that posed some difficulties in a multi-center trial.

Prehospital provider training. We used Webinar, PowerPoint review, and required mandatory testing to get our prehospital providers up to snuff with what we wanted to do in this type of trial, and there are varying skill sets and levels, whether you're looking at ambulance/prehospital or helicopter-based prehospital providers.

And, finally, the prehospital setting, you're taking an intervention to the prehospital setting. In our case, we have plasma, which lasts for 5 days, thawed plasma. So we're using a courier, and we're shipping it via courier, transporting this precious resource back to the blood bank so they can be used before 5 days so we can always have a fresh supply in our helicopter service for the month that they're randomized to plasma. So that's

been a difficulty.

I'm going to do the next multiple slides in 30 seconds. We also got funded to look at tranexamic acid in the prehospital setting. Very similar inclusion criteria. So the lessons learned part of this talk is that similar inclusion criteria for the PAMPer study, there is prehospital intervention and in-hospital intervention, looks at different dosages of TXA. But for the lessons learned, we provided our IND application what they wanted, and we were able to get an IND in 30 days, relative to a year, for the second trial.

So, again, with a little bit of experience -- and our primary outcome is 30-day mortality, again, because I gave them what they desired for that and we did that up front, and that certainly saved time and was more efficient. Similarly, our IRB, as well, suited to do our community consultation. We're just about done. And the second trial, looking at tranexamic acid in the prehospital setting, should be enrolling by spring of 2015.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Sperry.

I would now like to invite Dr. Thomas Scalea to come and give a perspective from a Level I trauma center. Dr. Scalea is a Physician in Chief at the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center and the Systems Chief for Critical Care Services in Maryland.

DR. SCALEA: Good morning. When the FDA people asked me

to come talk, I told them I'd be happy to do it. I said do you want this to be formal? They said no, you don't -- don't even bother bringing slides, so I didn't. But we'll take about 10 minutes, and we'll talk about my perceived barriers to doing this type of research, and because I had a fair idea of what Tim and Rick and Jason were going to talk about, I decided I would talk mostly about process barriers: Why do we have trouble getting this done, both taking care of the patients and trying to collect good data?

And it really, in my mind, falls into four categories. The first is we need more good patients to study, and certainly relative to the military trials, civilian trials are very different. Yesterday we did a nephrectomy on a 91-year-old lady on antiplatelet drugs in the afternoon and then did a lap for a gunshot wound to the abdomen later. Those are obviously two very different patients, and it seems unlikely that the same solutions are going to work for each of those. Yet that's my world. You know, this lady fell down the stairs, the 91-year-old lady on the antiplatelet drug, just -- Tim was talking about. And so we're going to have to try to suss all of that out in order to be able to figure this out.

We have systems of care that are supposed to drive the sickest people to the trauma centers, and that works right up until the time they're too sick to make the trip. So, if you get shot in downtown Baltimore, you've got about an 80% chance or a little higher of coming to us or Hopkins, so that's (a) pretty good, and (b) it's easy to study. Of course, you get out into

the community and you're too sick to get downtown, then you go to the nearest emergency department and that's -- I understand you don't want them to die on the bus, but the ability, then, to collect that data and to deliver the same quality of care is just not there. In fact, the absolute incidence of bad hemorrhagic shock is pretty low.

We just finished PROPPR, and we did how many patients, John? 690 or so, in 12 really busy trauma centers. Took us 15 months to get 600 patients from LA County and Houston and us and Harbor View. It's not that common. And then, of course, you add in the EMS time plus the emergency department time, particularly if the EMS time is a long time. And it's hard to accrue a sufficient number of patients even looking across the country to answer the question.

The second is we need more control over the care that's delivered. There are very few places that really can do good randomized control trials in the field. How many of them have been done for trauma in the last 20 years in the prehospital setting? It's not that many. As a matter of fact, it's very, very few. The emergency department care, depending on where you work, is different. Depends who's on call, who's working. The same thing is true depending on who's on call for trauma.

With lack of good Level 1 data, it's a little hard to mandate that it gets done this way or that way, though I think I do a pretty fair job of mandating how/what gets done. I expect Dr. Holcomb does as well. And

when we start talking about hemostatic devices, you now need to train a whole slew of surgeons, you need to maintain competence. You say, okay, well, the hemostatic bandages, how hard can it be? Well, you know, there's a difference between really packing the liver well and just grabbing some hemostatic gauze and shoving it up there. It needs to be done well. If you start talking about REBOA, this is an invasive procedure. We've designed a course. Megan Brenner, who is in the audience, did it for us.

We're giving the course, but we've really asked the question: How many do you have to do to be competent? How many do you have to do to maintain your competence? How do you benchmark this against accepted norms when now you're not doing an elective angiogram, the person's dying in front of you; what is acceptable complication rate? We don't know.

The third is I think we need better definitions of study parameters. Now, you know, it seems pretty easy except we went around and around for a while, even with PROPPR, before we decided who was in and who was out. And once again, you've got 12 very busy Level I trauma centers that deliver care mostly the same way, but it took us a long time to bang that out in order to do it. And the same thing is true with outcome parameters. Well, death. That's easy, right? It's binary. You're either alive or you're dead. It's really easy to study that, but is that the fairest test?

I'll tell you, this weekend we took care of the worst pelvic fracture I've ever seen in a guy that made it to the emergency department.

We used the REBOA, we used the hybrid room. I bankrupted the place for combat gauze. We ran out because I used every piece we had. This guy got 120 units of red cells in 12 hours and 100 units of plasma. And then he died probably as a complication, I think, of his factor VII and the tranexamic acid because all of his extremities died now. So he's dead. He's dead at the feet for the hemostatic bandages or the hemostatic maneuvers? I don't know. Not sure. But, you know, how many of those are we going to see this year? A few. And so getting our arms around that and really defining what it means, that the devices did their job is, I think, more complicated than saying the patients are alive or the patients are dead.

And then, finally, I think we need better ability to collect data. First, you need the money to collect data, and we are incredibly blessed because we have 24 hours a day, 7 day a week people in the resuscitation unit. Every patient gets seen by the study coordinators, every patient gets screened. And then they got entered, and PROPPR was very kind to us because that's what we used to pay them. And now, of course, PROPPR is over, and that's going to cost us a few hundred thousand dollars this year that we're going to pay for out of our practice plan because it's important to us.

Well, so you can pay the faculty, you could pay the study coordinators. It gets kind of expensive, particularly when you're between studies. We've decided we're going to do it. I think we're going to do it. But

it's kind of an expensive thing to do. IRBs are complicated, and we have a great IRB, and like Jason, we've done a zillion of these waived consent studies, but we're still -- this extended preservation/resuscitation Sam Tisherman clinical study, which is a great study and there's ultra-profound hypothermia, there's a way to control hemorrhage. We've been at the IRB for two years, and we are still -- I don't know how many times it's been sent back. Hey, we got new people on the IRB, could you start again and go through this yet again? And it's exhausting in order to get to do that. And then, of course, you need cooperation. You need cooperation in the institution, you need cooperation between institutions, and that's not always as easy to do as perhaps it should.

And so it seems to me that if we can solve those four issues: we need more patients to study, we need better control over the various facets of the time periods of care, we need better definitions of the study parameters, and we need better ability to collect the data. And if we can just solve those four little problems, then everything should be really easy to go ahead and do these studies.

I hope this was helpful.

(Applause.)

MS. KUMAR: Thank you so much, Dr. Scalea.

Well, as I mentioned before, I'm going to cut into lunch just a little bit, and I promise to still give you an hour, but I'd like to open it up for

questions for the audience, and maybe we can take about 10 minutes or so to do this.

But I had one question, I guess, to start. And we've heard the woes about doing these trials, and they're expensive and complicated, logistically challenging, and they take a long time. And we've heard that we need these studies postmarket, and it's great if FDA, you know, if they are cleared or approved with data, but that's not always the case. If it's so, it's great. What are the thoughts on doing some of this research premarket versus postmarket? What are the drivers for that? Where would the stakeholders in the audience -- question for the audience as well -- like to see these studies being done: premarket with FDA oversight such as a 50.24 study or otherwise, or postmarket? And does it depend on the type of technology?

DR. PUSATERI: Yeah, I think it's going to depend on the type of technology. I would hate to say that when we agree we need data, that that would change FDA's way of regulating something. And so personally, I would rather see maybe a program that has, say for a product that would not have otherwise needed premarket data, that the pathway would be the same but you could -- one possibility might be to require postmarket surveillance study. But because we're all agreeing we need data and then making more rigorous approval requirements, I think that would be, could be a mistake.

Of course, some products are going to automatically require a premarket study. But I think it will allow a lot more flexibility and in a way

reduce, from a company's point of view, the development risk by not adding a premarket study unless absolutely necessary based on safety and efficacy, FDA requirements. But I would still think that it's adding that impetus to perform the postmarket study would be a good option for FDA.

DR. ASHAR: I have a follow-up question to that. I was wondering, you know, as we decide -- you know, one of our initiatives or one of the strategic goals of the Center for Devices and Radiological Health is to strike the right balance between premarket data and postmarket data. So what you're proposing, what would the panel say would be the threshold of evidence that would be reasonable to allow premarket clearance or approval to have a framework that could support those decisions in the postmarket?

DR. PUSATERI: I have a suggestion. As an example, for these trauma devices where our studies, as discussed, may be extremely difficult, extremely expensive, require very long periods of time, I think a mix of -- this is a complete hypothetical -- a mix of animal and clinical data. I mean, I wasn't preferring no clinical data. But what I'm really discussing is a need for a premarket Phase I clinical trial, is that there could be different combinations for different complexities and invasiveness of the product. But I think it would still be a way to meet safety requirements, number one.

As an example, efficacy may be more heavily weighted on animal studies, maybe including primate studies. And then there could be another step in between where you say, well, we really do need a Phase III

type study, so maybe something along the lines of a very robust Phase II study that has the mix of the patient population, a smaller number, a smaller number because the idea would be here not requiring superiority over some other product; it's really meant to look for -- ensure non-inferiority and ensure safety in that population as opposed to a traditional Phase III trial requiring superiority over something else because some of these devices will be very difficult to get to patients or -- well, mainly it's very difficult to get to patients because some of these extreme cases are prolonged loss of blood. Very innovative products with very complex patients, it would be very difficult to get that exact population.

Another approach could be allowing initial approval in some complex surgical patients, but not specifically eliminating trauma. For example, you could have a mix of complex surgical patients for hemorrhage and then a later requirement to do a postmarket study in trauma. So I think there's a lot of options, and you can tell we've had many discussions about this in DoD and everyone -- the companies and others here who have thought about this realize how complicated it is; that's why we're having the conference. I think there are options below the standard Phase III clinical superiority trial.

DR. EMHOFF: Yeah, I would second that. You say what's adequate? I think you have to look at what are you trying to do? Are you trying to get a device on the market because -- and only say it's safe and then

let post-approval data then -- is it efficacious? I mean, look at Xigris. You know, we'd still be using Xigris if we didn't do -- you know, have to do market studies and it showed that it wasn't all it was cracked up to be.

So I think you've got to do both, but I think -- you know, do you have to go as far to say that -- and this is, like you said, superior to everything else and they'll stop doing everything you're doing and then let's only use this. I think there are a lot of ways to skin the cat here, and I think there's got to be some way to study something and say it's safe to use, but then require that you have to then submit data to show how good was it in order for people then to make some decisions about do I do this or not.

DR. KING: Yeah, I think we need to be careful what we wish for because you might get it. The audience and the panel, I think, largely agree that decisions need to be data driven. And when it comes down to what the requirements will be for a specific device, I think it ends up depending on the device. If you insist on a randomized premarket trial for every single intervention, you'll get nowhere, right? None of us will get anywhere. So that can't possibly be the solution. That may be the solution for certain devices, but I think the solution needs to be tailored to the intervention.

So the intervention that has a reasonable risk/benefit profile or a reasonable assurance of safety for someone who's going to die otherwise, it might have a very different set of approval characteristics or an approval plan than something that's extremely or moderately high-risk but intended for

someone who is not dying, right? Those are that -- very different pathways. So, yes, we all want data, but we have to be realistic in how we're going to get that data because if you set the bar too high, none of us will get anywhere.

DR. MARCOZZI: I have one follow-up. I think there is also a pipeline -- and I mentioned in my talk -- around how the special operations for the military community and FDA could have a standard formalized discussion or a standardized group that actually gets together. I think this is a question for them on -- you know, we've used it three times, because the special operations community has the ability to utilize end-use devices that potentially aren't in the eyes of the public, and they're using things maybe three times, and in all three times they've been successful. How does that discussion inform FDA and get the product out to the civilian market?

And that's some of the challenges between the military and the FDA that I think that -- not that I think, that I know have been a sticky point since 2011, 2010, that there was -- DoD and FDA were having some challenges. I'll let you know that it wasn't FDA on one product. FDA was very receptive to DoD. It was DoD trying to get itself streamlined and right. So it's not all the FDA; it's multiple compliance.

UNIDENTIFIED SPEAKER: That actually leads right into my question, which is taking a step back from any individual agency. I think our country has had a very robust discussion in the last, I don't know, five

decades about the ethics of performing research. And I'm wondering, you know, the PAMPer trial is a great example that we now have quite a few roadblocks in place, so besides the FDA exemptions that are required, the IRB approvals, the community consent issues.

In my field, which is blood products, there are also exemptions required from AABB. All of this together is a huge burden, regulatory burden, from multiple different agencies, and I'm wondering if we should have an equally robust discussion in our country about the ethics of not doing research in the cases where you have a patient whose mortality approaches 100%, if not treated -- I mean, a patient population. Or in the cases where you already have a drug or a device on the market and you don't have all the data you need in order to evaluate it.

MS. KUMAR: Thank you.

Binita, one last comment, and then we'll break for lunch.

DR. ASHAR: I'm looking forward to having a crack at the panel after lunch. But I think I would like to revisit this discussion. I think it is the crux of what we're trying to accomplish.

You mentioned, Dr. Emhoff, that it really depends on what the threshold is for regulatory clearance or approval, and I think, essentially, you know, this is very -- you know, this is not regulatory speak; this is translating what I know into something that could be helpful in the discussions, and that is we're looking to see if the benefits outweigh the risks, and you would make

that decision on a case-by-case basis after all of the patients that you've seen.

And so after lunch I'm hoping that the panel might be able to comment on commonalities in the body of evidence that you've accumulated in your experience about what patient groups, how they may be stratified so that benefit/risk in one population can help guide the threshold of evidence that we would like to see as device development occurs.

Thank you.

MS. KUMAR: Okay, thank you.

We are going to reconvene after lunch at 1:15 p.m. There are concessions available. If you ordered a box lunch, they should be able to be picked up at the kiosk. There's also a speaker ready room, which is called the press room to the left of this room, if anyone would like to go back there and eat their lunch.

Thank you.

(Whereupon, at 12:20 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

MS. KUMAR: We are going to continue with Session II, which is to gain a better understanding of the unmet trauma care needs.

Opening our afternoon part of that session will be Dr. Kevin Prohaska, who is with the FDA in the Office of Good Clinical Practice, and he will be discussing 50.24 studies.

DR. PROHASKA: Okay. Let's go ahead and get started. First of all, I'd like to thank the meeting organizers for inviting me to speak today on this very important topic. This is something that is near and dear to my heart. I'm a medical physician, ex-military, ex-Army. I was deployed in the first Gulf War. And I can think of certain patients or subjects that I could have saved had I had some of these products that are being discussed or some of the concepts had been resolved way back then, 20-25 years ago I guess it's been. But today what I'm here to talk about is the regulations at 50.24.

I'm going to give a general overview of the regulations under 50.24. This is the regulations that govern the conduct of research in which there's an exception from informed consent in emergency settings. I was touched by the comment made by Dr. Sperry earlier, prior to lunch, where he said his first bat at this took almost two years to be able to get it finally reviewed and approved and get started, in part due to -- some of the regulatory hurdles contributed to the requirements under 50.24. That is, of

course, sad to hear. And what was nice to hear, though, is that his second time at bat, the first time he went through the FDA, got reviewed and approved within 30 days, which is fantastic.

So there are a lot of requirements under 50.24, and they're important to understand. And it is very important to understand why they are there because, in fact, what we're doing in this type of research is denying individuals the right to choose for themselves whether or not they want to participate in this clinical investigation, for obvious reasons. Certainly, they are not in the position where they can say yes or no, but there needs to be appropriate safeguards to assure that their interests are protected. And this set of regulations hopefully summarizes what most people think is a reasonable set of protections.

So, first of all, the regulations became effective in 1996, and since that period of time, there's been approximately, I'd say 100 or so applications to the FDA. A large percentage of those applications had been, for one reason or another, placed on hold. I don't have the information as to why the various holds were put in place, but I would say that it's not easy to get through the FDA process, if you will. And it's evident by Dr. Sperry's experience.

What's required is that when these applications or these protocols are being considered, they need to be submitted to the FDA under a separate IND or a separate IDE. And the reason that that is the case is

because the FDA needs to be given 30 days in which to review this. And the studies are not permitted to proceed without prior written authorization, as is often the case with the first study submitted to any IND.

IRBs also have to have a slightly different makeup than they usually will have, although this is often the case, that they have to have a licensed physician who is a member or a consultant to the IRB who is not otherwise participating in the research.

And the sponsor must report IRB non-approvals to the FDA and also hopefully information as to why they didn't approve it, because the FDA will need to consider that.

And then what follows is a long list or approximately 12 or 13 different items that the IRB needs to find and document. The IRB has a big task ahead of themselves, and not all IRBs are well versed on this matter, so it is important for the sponsor, the clinical investigator, and the IRB to work together so that the IRB can get what they need in order to make the approvals that they have to make or the determinations.

First of all, there has to be -- the IRB has to determine that the subjects are in a life-threatening situation. Now, in the issue of severe trauma, that's usually a bit of a no-brainer, if you will, but that argument has to be provided to the IRB so that they can make that determination.

The other one that's probably a little bit more difficult is that available treatment is unproven or unsatisfactory. In the situation of

noncompressible bleeding, that's probably relatively simple to provide. But in other clinical situations, that is likely a little bit more difficult to provide to the IRB.

And then the third thing is that there has to be valid scientific evidence necessary to determine the safety and effectiveness of the intervention. So there has to be some rationale provided to the IRB to help them understand why there might be some benefit in conducting this research. It may be animal data, it may be early human studies or maybe anecdotal experience, but whatever it is, it needs to be summarized and provided to the IRB. Also to the FDA, of course, as part of the IND or the IDE application.

Another determination that the IRB has to make is that obtaining informed consent is not feasible because the subjects are unable to give informed consent as a result of their medical condition. This usually means that they're unconscious or they're exsanguinating in front of you and that type of thing, that the information -- rather, the intervention must be given before consent can be obtained from the legally authorized representative. Now, in the military setting, when you're talking about deployed soldiers, that's usually pretty easy to discuss. But in the civilian sector, where you conduct it in an emergency room where LARs may be more readily available, that might be a more difficult argument to make. And then the other thing is that there is no reasonable way to prospectively identify

individuals who are likely to become eligible. This relates to the issue of pre-consenting individuals who may become likely for this intervention, whatever it may be. That may or may not be feasible in this type of study, but in certain indications it may be.

Another determination, No. 5, is that research holds the prospect of direct benefit to the subject. This is critically important. There has to be good rational argument as to why the subjects are likely to benefit from this therapy. And, in fact, you know, subjects are facing a life-threatening situation; either the preclinical data supports the prospect of direct benefits and the risks of the research are reasonable in relationship to what is known about the condition, the situation of severe bleeding -- you know, death is the ultimate outcome. And so a certain significant amount of risk is likely to be acceptable, but it really needs to be mitigated and discussed appropriately.

The other piece that the IRB has to make a determination on is that research cannot practicably be carried out without the waiver. This usually means that -- not necessarily for rare conditions, but also time can be of essence. Let's say, for instance, in a clinical situation in an emergency room where it's a small community hospital and they might see this case only once a year. It's not likely you're going to be able to do the research there and that kind of stuff and so forth.

The protocol: This is where a lot of INDs, at least, sort of forget

to provide is that the protocol needs to define the length of the therapeutic or the potential therapeutic window based on scientific evidence. Often, from the clinical investigator or the sponsor's perspective, this is self-evident, but it really needs to be discussed clearly in the protocol that's submitted to the FDA, but also to the information submitted to the IRB, and this can be based on animal data or it can be based on anecdotal data, if necessary. But the more scientific it can be, the better.

And then the PI, the clinical investigator, has to be committed to attempting to contact a legally authorized representative within that therapeutic window, whenever possible. This is part of the protocol that needs to be stated as well. Again, it's another one of those protections that are important that are used in lieu of informed consent. Now, of course, it's not always possible, and we don't want you to exhaust the entire therapeutic window trying to contact legally authorized representatives. You've got a patient in front of you; you need to take care of them. You take care of them. But you do have to have a plan to contact legally authorized representatives as soon as you can, and you need to document that plan and make it available to the IRB whenever they do their continuing review and so forth.

Another piece of information that is critically important and often left out, or occasionally left out, I should say, is that there does need to be an informed consent document, although there may be no chance of it possibly being used in some situations, like a battlefield situation perhaps. It

still has to be part of the application and part of the information submitted to the IRB in case there is an opportunity to get informed consent from an individual. And it has to be written in the typical way that an informed consent document has to be written, and it needs to have to satisfy all the requirements under 50.25, I believe it is.

And then the IRB has to review and approve procedures and information that is used when providing family members an opportunity to object to participation. Oftentimes this comes after the therapy is used in an acute situation, but for whatever reason the family might want to withdraw the individual from the study or the research. Again, it may not be relevant in the combat zone environment, but in an emergency room setting in the civilian sector, it certainly may be relevant. The information that is provided is usually analogous to the same information that is found in the informed consent document.

Then the IRB needs to ensure that the following additional protections are included in the materials that they reviewed, and this again has to be or should be submitted to the FDA. The community consultation plan has to be provided in the information given to the IRB. Now, there was talk about how different communities may want a different plan. That may be appropriate, given the local context in which the research is being conducted in various locations within the United States. However, it's not uncommon for sponsors to develop a template which is used across the

country in multiple centers which may be modified by the different IRBs. That sort of helps facilitate the research going along rather than having each one develop it de novo.

Same thing with the public disclosure for the studies prior to the onset of the study. Same things. Sponsors frequently, almost always, develop these plans or at least the draft, if you will, and then they're reviewed and approved by the local IRBs which may modify them for their own local needs. But you can facilitate that by having a good template with, hopefully, all the bells and whistles that most IRBs are going to want.

And then afterwards, public disclosure. This has to do with study results, which the regulations also include a requirement for demographic information to be included in what is disclosed publicly. And this, again, relates to respect to the individual. You want to let them know that their contribution to the research, them or their family, that their contribution to the research had value, that it really furthered the science, if you will, even if it's a negative study, which unfortunately happens. That information is important because it helps further the science in the long run.

An important piece of this is to have an Independent Data Monitoring Committee that has oversight responsibilities over the research. And then, again, the clinical investigator is committed to contacting the subject's family within the therapeutic window, if feasible.

I think this is the last one, 12. They assure that procedures are

in place to inform the IRB and inform the subject's legally authorized representatives and family members of the subject's participation in the research as soon as possible. So after the intervention is done, even when the patient dies, the family members need to be informed about the research. And that plan needs to be pre-stated.

And, again, the details are typically the same ones that you would find in the informed consent document, and there has to be assurances that subjects may withdraw at any time without penalty, so if there is ongoing intervention or ongoing collection of data, at the point which you talk to the family or the subject, subjects do have to have the right to be able to withdraw at any time, provided it's safe for them to withdraw. And you need to have a plan be reviewed.

So what needs to be submitted to the FDA? Basically all the same stuff that needs to be submitted to the IRB, because we have to look at that ourselves, if you will, to make our own determinations. Again, there has to be a separate IND or an IDE. You may reference previously submitted data, so you don't need to necessarily clutter the application with a bunch of stuff that can be found elsewhere, but we do need proper identification of where we might find that information.

And then you have to address the specific things that are found under the 50.24 requirements, such as the plans for community consultation and public disclosure. The justification for conducting the study in subjects

who cannot consent; that is critically important because this is something that helps us decide whether or not this is an appropriate approach for this particular type of study. A description as to why existing available data is unproven or unsatisfactory. A rationale for the therapeutic window. A description of the various commitments that the clinical investigator has for contacting LARs or family members. And a copy of the informed consent document should be submitted.

I'm going to skip this because time is short, but as far as drug studies go, even when they're exempt from the regulations, they need to be submitted to the FDA under an IND in order for them to be reviewed and approved before they can be conducted if it involves exception from informed consent.

For devices, there's a very narrow group of devices in which an IDE is not required, and that has to do if the device is being used with its approved indication in a consistent manner with its labeling. Very rarely would it probably affect exception from informed consent. If you think that's the case, you should contact CDRH.

So my recommendations: Work very closely with the IRBs and provide them all the information they need. And the IRB review should probably occur after the FDA review because there is probably likely to be some fine-tuning and tinkering to most of the protocols. And the IRB should get a copy of the FDA's written determination prior to approving the

research. Again, these are recommendations.

Now, all of these additional protections that are outlined in 50.24 are built on the principles contained in the Belmont Report and the respect for persons, beneficence, and justice. This is not a bioethical conversation, but the primary problem here is informed consent is missing from this paradigm, and we need that, something to take the place of what is missing, and those are the protections contained in 50.24.

I know they're bureaucratic, I know they take time, but they're important. They're very important because there's probably nothing more important to the conduct of research is that it be conducted ethically. And there is nothing more damaging to an organization or an institution is to have their ethics be in question, if you will, in a public venue because these studies, by their nature, have the tendency to be very controversial because you're not getting informed consent.

I'll skip that.

And then resources, I've got them listed here. Again, you can contact me. My information is at the end. But there's excellent guidance, it's 55 pages long, that FDA published in 2011. It's very well organized, I think, and it gives you a lot of good information on how to get through this process, hopefully easily. Then, also, you can go to the dockets, and the information on how to go to the dockets is there. If you want to look at how other organizations have handled public disclosure, much of that information is

there. And then, of course, I do recommend talking to the review division.

There's my contact information.

(Applause.)

MS. KUMAR: Thank you, Dr. Prohaska.

So, to share his experience with conducting multiple 50.24 studies, I'd like to invite Dr. Holcomb back up to the podium.

DR. HOLCOMB: All right. Well, I am not going to talk about the experience with 50.24 studies because that would take a long time. What we'll do here is go there.

So the title of the session is really about data, and the data are really lots of data. There are lots of questions. I was asked a couple of questions here, and I thought I would just really go through these questions and then speak to them.

What are the implications for labeling for military use only? This was brought up briefly in the last session. I think the implications are substantial, and I think they're probably unintended. I would say that on the battlefield, even in the height of the war in Iraq and certainly going back in my experience in the military, deployed many times over 23 years and now working in the civilian community, the needs in the civilian community and the needs in the military are almost exactly the same. The wounding agents are different. Even in the worst environment in the United States and most western countries, you don't have IEDs and high velocity weapons being the

norm. They certainly do happen, but they're not the norm.

But once wounded, as I showed with the picture earlier this morning or this guy, who has a low velocity gunshot wound through his liver but was dying, near death, when we saw him and I put a Foley catheter in his liver to help stop the bleeding -- he did okay, left the hospital in 8 days. But those patients are -- once wounded, the physiology and the time to death, the diagnostic tools, the intervention tools are remarkably similar despite the difference in wounding.

Now, what is also true is, as we talked about earlier and Colonel Rasmussen showed these data with 50,000 injuries and 6,700 deaths or almost 7,000 deaths, I think, that's over -- as he said, over a decade of war. Yet during the same timeframe, there's been almost a million deaths from injury in the United States, almost a million deaths from injury in the United States. And I stand up here as a retired Army colonel. I'm not minimizing the deaths on the battlefield in any way, but from a public health point of view, a million deaths in the United States is a big deal, it's a big deal.

And, again, wounding agents are different, but, you know, Colonel Rasmussen is there in uniform, but the physiology of Howard Champion in a civilian coat and tie right next to him is pretty similar. You know, if I shoot him in the aorta --

(Laughter.)

DR. HOLCOMB: -- and I shoot him in the aorta, both of them

need an aorta device, right, to stop the bleeding despite one being the military and one being a civilian. I know, it's somewhat trite to do that. But there are a lot of bleeding patients in the civilian world, and that's just not the United States; it's around the world.

You know, where do you go first with these devices? Maybe it makes sense to go first into the military environment because we want the guys out there in Afghanistan in caves and on and on to have these devices, but if we use dried plasma, which was talked about earlier, to the best of my knowledge, it's been used four or five times in the last 18 months. It's not really an experience.

And that required the White House to get involved to get that thing approved. And it's only approved for a very small group of specially trained, highly trained military medics who, by the way, their units have the lowest casualty rates. Why? Because they're highly trained special guys. So the guys that have the highest casualty rates on the battlefield and the least trained medics have the less good stuff. But once you start going down this pathway, you hit really cognitive dissonance, right? And then you say, well, I got it on the battlefield, but I don't have it all over the streets of Baltimore and Houston, wherever, and across the United States where there are millions of injured people every year and 150,000 deaths from injury.

So military use only is a big deal. It also gets to training as well. If you have it for battlefield use only, then the interpretation -- and some

people in the military say you can't use it back here in the rear of the train. So the same high-speed military medics that go into the field go train in civilian trauma centers, they can't train with the thing that they're going to be handed when they hit the battlefield. That's unintended. Nobody intended that. But I would say that these words are really important.

I covered a lot of this already. What's the difference in the operational environment and the civilian environment for product development and translatability of data? We talked about data, we talked about injuries. You know, the more patients I take care of -- I took care of a lot of casualties on the military side, I've taken care of now a lot of casualties on the civilian side in the last six years. There are many more similarities than differences, many more similarities than differences.

One of the big differences, though, is that 80% total body disruption on the battlefield that several speakers discussed, people literally blown to death, blown to pieces, reassembled by DNA. You know, when you go look at the thousand autopsies at the AFIP like we did, there's a large group of people who are not going to work good, but that 20% -- and their epidemiology has been described very clearly -- now become a little bit more similar to what we see in the civilian world. It's interesting.

Civilian world and military world has experienced medics and not-so-much experienced medics. They have small centers and highly capable centers. You know, you can call them Level 4's or whatever, non-

trauma center; same thing on the battlefield. Short evacs and long evacs. You get hurt down in the valley in Texas, it takes you 6 hours to get to my hospital; 6 hours, right? Or you can get hurt right around the corner, and it may take you an hour because it's rush hour. You're only a mile away in Houston; it takes you an hour to get in to me. Once injured, very similar physiology. We've talked about these other differences as well.

Are there different paradigms for use in the civilian versus military practice? You know, I really don't think so. There are some different injuries you see on the battlefield that are more common. People talk about this, more common or less common. Well, it's a more common injury of those injured on the battlefield that have the junctional hemorrhages, but if you look across all 30 million people injured every year in the United States, there are more common junctional injuries in the United States, but there are 5,000 hospitals that they go into. So each hospital may see or each group may see less injuries. And then do we want to get these things on the battlefield and in the civilian world as soon as possible? Absolutely. I think we encounter that more and more and more.

How do we get more data? So I was asked to go to an NHLBI meeting about a year ago, actually June of last year, so 14 months ago, and we talked about different devices, and we talked about truncal hemorrhage specifically.

I showed that slide that I showed this morning. There are a

couple more new devices, I need to update that thing, but a lot of people focus on stopping bleeding.

How do we get more data? Well, this is Don Trunkey's slide and somebody showed the trimodal distribution of death that he created in 1983. This is in *Scientific America,* and this talks about funding and impact of disease. So this is life years lost, 1983, and this is funding for trauma versus cancer and heart disease.

This is Peter Rhee's paper. These are life years lost; it's only gotten actually greater and trauma injuries have gone up, as I showed before. Funding for cancer and heart disease, in the multiple billions. Billions for HIV, which doesn't even make the list on the CDC website as a leading cause of death. And then injury down here. So how do you get more data is you do more funding. That's not the focus of this meeting, but it needs to be stated very clearly.

And then I think providing some solutions. Some of our FDA colleagues said, well, what you do? Well, what I would do with many of these devices is probably study about 50 patients. I would do it in an observational postmarketing fashion. I would use the American College of Surgeons TQIP program, the Trauma Quality Improvement Program, that right now is used at 198 centers. It's risk adjusted. I would use it in a research mode with those 50 patients at, say, six centers across the United States. If you're deploying one of these devices, limit it to six centers. Make them put their data into a

TQIP in whatever database, you know, they need to do. Don't make them submit to 10. And then you could do risk adjustment before and after with TQIP. You can also do three-to-one propensity matching, so you can get concurrent and retrospective data using the Trauma Quality Improvement Program that trauma centers already utilize.

We're going to try to do this in our upcoming nine-center observational prehospital blood product study done on helicopters, so we'll have five centers that have blood products on helicopters and four that don't, and we're going to use TQIP in this research mode to kind of try it out and we'll see what happens.

Key point: Post-approval only because of the consent mechanism discussed already. I have done three of these 50.24 studies. It's very doable. It is a mechanism, but it would be difficult, I think, to do for a 25- to 50-patient study.

This has been covered already.

Thank you very much.

(Applause.)

MS. KUMAR: Thank you, Dr. Holcomb.

I would now like to invite Dr. Ben Eloff up from our Office of Surveillance and Biometrics to discuss some of FDA's experience with using data registries.

DR. ELOFF: Thanks. I'd like to thank the organizers for inviting

me. I feel like a lot of this, this morning and prior conversation, has been all for setting me up for this talk, which is a good place to be. So I want to talk a little bit about what we do on the postmarket side of things in our Division of Epidemiology.

First, I'd like to talk about the total product life cycle and how medical devices are developed. This is the new way of doing it. Used to be just one circle, but now we have a circle and a line. And you see all the way to the right of the figure, the postmarket monitoring. That's traditionally where we see registries and observational studies being used for most medical products. And, clearly, that's where a lot of focus is. But as we just heard from Dr. Holcomb, you know, you can use registries and observational data sources really in any phase of development of medical products.

So what I like to think about a registry and these observational data sources is really as the base of the pyramid where you get that basic registry data that can be used for quality improvement, for surveillance, for retrospective studies, so on and so forth. And you see to the right of this, I've got where our various laws and regulations fit in. A lot of that is covered by HIPAA when it's non-research use, although it still gets reviewed by the IRBs. We get up into the public health trials, that is a trial done not for FDA purposes. Since we're in the FDA, we do public health plus. So there you have your Common Rule issues. And then, of course, stacking on top of that pyramid even more, you have the 21 C.F.R. Part 50 and the Part 11

compliance and so on that's needed. But I want to say that none of these regulatory hurdles is unsurpassable. In fact, we've got examples of studies that have been done in registry building upon that and meet all sorts of -- with public health purposes and FDA purposes.

So where does our interest in registries at FDA come from? We've been working with registries of various different types for many years now, and in the fall of 2012 we issued a report that called for the modernization of a national system for medical device postmarket surveillance. At the center of that is really the development of national and international registries for medical devices and having a unique device identifier for each of those devices incorporated therein. But you'll notice that that's just the center. There are so many other data sources that are available to us that we can make use of to really understand the ongoing development of safety and effectiveness profiles for medical devices, both in the premarket and postmarket spaces.

So that 2012 report called for four pillars of the device postmarket surveillance system. The first is to establish the unique device identifier system and promote the incorporation into electronic health information. So the UDI rule went live last September and is going into full effect this month for Class III devices, life-supporting/life-sustaining devices that are in any class required to have UDI on them by next year; Class II devices, the year after; and then Class I devices, two years after that.

You'll see the second pillar, very germane to what we've been talking about today. It's promoting the development of the national and international device registries for selected products. Now, a registry is a great thing, and I've been working with them long enough to understand all of the positives, but I also understand all the negatives. Registries are not a one-size-fits-all solution. I mean, think about where you have a device or an exposure to a medical product that you can clearly identify, such as one of these hemostasis devices.

You know you used it on a given patient versus, let's say, a scalpel, which is also a medical device. But you don't know which scalpel you used or which brand it was or anything like that, and it's not going to get captured in your registry or in administrative claims or in billing records. It's going to be impossible to do that, and frankly, that's not a high enough concern for us to put the money and effort necessary into building a registry. So you want to focus on where the highest bang for the buck is.

And you'll see the third and fourth pillars actually also benefit from having registry infrastructure in place and modernizing adverse event reporting and analysis. Currently, our adverse events reporting system is denominator-less. We get ad hoc reports, and really, we get them without context of knowing the exposure to medical devices. So you tell me that you've got 10 events in a given device. Well, is that out of 100 exposures or 100,000 exposures? It makes a big difference as to whether the alarms ring

and make us take action on that. So having a registry in place in which we can contextualize adverse events makes it very -- it makes our surveillance system that much more active and really, again, focuses the resources of the community on taking important action where action is needed.

And then, finally, developing and using new methods for evidence generation, synthesis, and appraisal. So having a registry there as an infrastructure in which data can be developed is very important. But how do we do new analysis methods? Can we use new ways of calculating propensity scores, for example, dealing with missing data, bringing together new methods for combining different datasets, so on and so forth? All of this really goes together.

So, to address this, the FDA has established the Medical Device Epidemiology Network, MDEpiNet, which is a public-private partnership that really spans the globe as being a leader in development of innovative data source development, analytic methodologies for medical device surveillance and research, really to advance patient-centered outcomes. And MDEpiNet -- I'll put in a plug for our meeting on October 14th, 15th, and 16th -- is really a collection of a lot of different partners who come together from many different walks of life and different sectors in healthcare delivery ecosystem focused towards improving outcomes for patients receiving medical devices, all coming from different perspectives. Some want to improve quality of care for their patients or understand cost effectiveness, comparative

effectiveness. We come from wanting to understand the exposure and outcomes related to medical devices, but all of these together really bringing together that infrastructure and new methodologies towards understanding medical devices.

So we've been doing a lot in the last few years to -- that move forward with this registry development pillar. First is the use of existing registries for post-approval studies and surveillance efforts. We've been involved in the INTERMACS registry for VADs, Total Joint Replacement Registry in orthopedics, also working with Australia and the UK for joint replacement and, of course, the new Transcatheter Valve Therapy Registry.

We've also worked on facilitating new registries in AEDs, speaking of ethics research. Again, the TVT; the IMPACT Registry at ACC in pediatric devices, pediatric cardiovascular devices; PROFILE for anaplastic large cell lymphoma; National Breast Implant Registry; Pelvic Floor Disorders Registry. All of these serve multiple purposes. One is they serve our regulatory purpose, which is the reason we're involved in them. But they also serve the societies, the professional societies, and public society at large in understanding and developing those best practices for delivering care.

We also have a strong regulatory science research program, and we've used existing registries for discretionary studies. Of course, that has to go through the IRB processes, as mentioned before, but these are excellent datasets that we've been able to apply that second part of the

pyramid to with the ICD and STS and, again, National Joint Replacement.

What's really exciting, though, is moving forward, we've been exploring registry capabilities in active surveillance, so going out and looking for and establishing networks such that we can actively surveil and collect data with the Data Extraction Longitudinal Trend Analysis system, which has been put in the Massachusetts hospital systems and across the American College of Cardiology registries.

We've also looked at linking studies, linking a registry directly with patient identifiers to CMS claims in the case of TVT and then receiving line level data here at FDA to do analysis as it comes hot off the presses, so we get the fastest access to data possible and we can take action and notify with the company there, with the societies there, what's going on and get a handle on it before having to take a regulatory action, waiting the months and all to -- while patients are being exposed to a potentially faulty device.

We've built the international consortia for orthopedic and cardiovascular registries, and those are building forward, and we're working with international consortia for breast implants and other registries as well, which is truly exciting. So we can multiply our effective sample size, given that medical devices, again, as Dr. Holcomb mentioned just a moment ago, physiology doesn't change from chair to chair or from field to field. It also doesn't change a whole lot once you cross our border, so understanding that medical devices are all manufactured by the same plant and shipped

worldwide and implanted in patients who are getting them for more or less the same indication, we should be able to surveil across the globe and really benefit global public health.

I mentioned that we've established a Grant of Authority under HIPAA to -- well, I haven't mentioned -- the University of Washington to collect AED and patient outcome data. This is a novel way of doing surveillance. It gets us access to direct data, but also really facilitates that conversation with the local IRBs and local EMS services, in this case, to provide this data and know that it's going to FDA for public health surveillance purposes and the registry linkage with TVT.

And then one thing that's really exciting is that with the ACC/STS TVT Registry, we actually did an analysis of that data and from the observational data were able to actually expand the Edwards SAPIEN valve indications based upon the registry data. I mean, that was just a great use of where registry data is not a liability, but actually a great asset.

So, with all this, this poor girl is not being sprayed by a fire hose, luckily, but you get the idea. We are truly drinking from the fire hose when it comes to data, and no registry data talk is complete without this type of image.

But, again, we've been developing the big data analytics capabilities, so you can see where we've been for the past 30, 40, 50 years in that discrete data. You know, an individual file comes in, we deal with it. You

know, an individual adverse event report comes in, we deal with it. An individual study comes in, we deal with that. We've now developed the High-performance Integrated Virtual Environment at the Center for Biologics, which runs on the supercomputer resources we have here at FDA. We're incorporating new datasets into this every day, getting down to the line levels, and we're looking to be able to make those connections between different datasets and find where signals exist. And this is all going to lead to enhanced and faster and better contextualized regulatory decision making.

I just want to leave with a few gaps that we still have. One is the interpretation of current federal regulations (particularly Privacy and Common Rules) by various IRBs has created significant obstacles for existing registries and for research.

The new trial designs and data sources rely also on the development of the methodology for analyzing the data collected.

The rules and regulations regarding direct FDA access to data need to really be developed in concert with the pre- and postmarket review procedures. You know, often we get summary data, and with our analytical capabilities, we can make use of the data.

I just want to make the plug for the partnership side. Effective public health analysis in the big data era really requires robust and active collaboration amongst all stakeholders. That's everyone in this room, everyone who gets their hands on these meeting transcripts and notes and all

of that. It's going to require all of us to move forward in this space.

Thank you.

(Applause.)

MS. KUMAR: Thank you, Dr. Eloff.

And now I'd like to invite Dr. Rasmussen, Lieutenant Colonel Rasmussen, back up to conclude Session I [sic] before we start our panel session.

DR. RASMUSSEN: So we have until 1:15 to do our panel, and as you've heard, perhaps by either members of our panel or those in the audience, there is a practice that's called damage control operating, and that sometimes is referred to as abbreviated operating. And for the sake of time and to stimulate some good discussion and question and answer, I'm going to do something called damage control presentation.

(Laughter.)

DR. RASMUSSEN: And I'm going to spare you all of my slides, but you have to listen to four points. So I'm sort of pulling a Scalea.

I'm going to say, with regards to data, that we want -- the question is do we want more data, which I'm weary of big data. I've had more people ask for data and do less with data than I see people do with it. Or do we want the right data?

And I want to just say four things:

One, the immediacy of need has driven the military to identify

and use the right data, okay? There's been immediacy of need. It's not for the general scientific interest. It's been a gap-driven immediacy of need for right data. That data has been put into the military's continuously learning health system, which has as its core implementation of that data into performance improvement, which is assessing how it works, how it doesn't work, and then going back at it and making that a dynamic process. So there's immediacy of need, the right data. The military's continuously learning health system, which -- I won't go into that right now.

And then the fourth is a good dose of focused empiricism. And for those of you who aren't familiar with focused empiricism, I would encourage you to look that concept up. And that really comes from the engineering field of just observing what works and so not going overboard to a grade of level or high level of data, but finding what works. And the military has used focused empiricism in its continuously learning health system in combination with the right data and then combining that with an immediacy of need.

And I'd like to stop there, Allison, if that's okay, if everybody listened. And I won't go through the slides, but I'd be more interested in maybe some discussion about some of the questions that John Holcomb presented and that were presented by the panel. I certainly can go through the slides if you want, but I think it might be better to address some of those questions.

So maybe I'll start since I deferred --

MS. KUMAR: So before we get started, the previous speakers that presented right before lunch in Session II, if you would also like to come up to the table to join in the panel discussion, we would appreciate that as well.

DR. RASMUSSEN: So as they come up, I think I'll have you just defer the talk. I'll answer one question that John presented, and I think it's been touched upon at various points throughout the morning, and that is the implication of labeling for military use only. And John did a nice job, I think, of presenting some of the implications. I think one implication that was not listed is that that labeling potentially or substantially limits or even kills the business model for some of these devices. So we go head over heels trying to get military use only thinking that that's a great success, and then we get that approval, and then there are no injuries to use it in, we don't really know if it works in humans, and it's very difficult then to study.

It's vexing, then, for the company that developed it, it's vexing for the military that paid for its development, and then we're challenged. And I'm not trying to overstate it and may be exaggerating, but John, I wanted to add, that was -- you know, you answered nicely the implications of military use only labeling, and I wanted to add that there's a potential for it, not always to limit or even kill, sort of, a business model that would take this beyond the military paying for supporting it. I'll stop there.

DR. ASHAR: Yeah. You know, actually I think that's the best place to start, and so I'm glad that various people have brought this up already. I think it's important to note that -- I think Dr. Holcomb said in his talk and I think it really crystallized things and that's where to start. You know, well, I guess the military would be the place to start because perhaps there is a need there, but if it's not -- you know, the military isn't the place to start, then it kind of goes to the question that was posed to the panel before the break, and that is, in your experience, what is the right place to start?

Recognizing that we have limitations in our bench and animal testing, and limited capabilities of testing human subjects and not -- unfortunately, we haven't completed, established, this learning infrastructure where we can constantly obtain feedback through registries and all streaming data sources to instantaneously improve our practices. You know, where do we start? So that's one question.

And I just want to, you know, caveat the fact that while we're -- I don't think anyone's particularly happy with a military only indication, but what it is, is a place to start. And that is a place to move forward from; it's not the end of the story. So, if the panel could comment on those issues, I think it's worth drilling down.

DR. EMHOFF: I'd like to take a stab at that. I think the place to start is first define the need. What is it, where is the gap, what is it that -- what's the problem? And that, I think, by trying to develop answers to that

problem, military versus civilian, I really don't think that's the way to go because then that allows you to be sloppy. I think the indication is an indication. Just because someone's wearing a uniform doesn't mean that the indication is any different. Now, you may be seeing a propensity for a certain injury or a certain type of injury in one sector or another, but that doesn't mean it's going to change tomorrow.

So I think you need to be very vigorous about what the indications are because as someone said this morning, you know, these devices and things that you're using, you're using it under extremes, whether you're civilian or military, and the decision-making process is not going to be very clear. There's a high likelihood that if the indications aren't clear and the training isn't the way it should be, that you may actually do some harm.

So I think you've got to be very clear on what it is you want to get done, what's the indication, what's the gap. And, number two, very clearly defining the indications, and that can be universal.

DR. ASHAR: Yes, please.

DR. HOLCOMB: So I'd do both. I don't think these things are to exclusion. I would -- as you guys have done, working within the framework or the rules that you have, I would get these devices on the battlefield as soon as possible. These guys are widely dispersed. I mean, you know, they're in, at the latest count, 60 countries around the world and with few incidents right now, but in extremely austere environments. And the recordkeeping,

while we've all worked hard to put together a trauma system and a trauma registry and research team, you know, it's just not as robust as you can do back in the civilian world. At the same time, I would do something in a postmarketing approval somewhat, you know, with a number of patients and then utilize these registries that have been discussed and allow risk adjustment, and before and after, and concurrent propensity scores with 25 or 50 patients, and so you'd have the best of both worlds within which to make the decisions.

And you'd get some data in pretty quickly. Some of these devices have gotten approved for military use or approved on the battlefield and have had very, very low rates of use, so we really -- and then none in the civilian world, right? None with an approved FDA device or product. So we don't know if they work or not.

DR. RASMUSSEN: I agree that's where you start, but they shouldn't be mutually exclusive. I mean, there can be two parallel paths to approval and clinical use. Certainly, military use only -- it shouldn't be military use only. It should be military use, and then there should be a backup plan for, when feasible, to get it into -- the ability to make observational study and use in the civilian setting, you know.

I think there have been instances, not uniformly, but instances where the military use only has been viewed as the end gain, you know, and then the other regulatory, sort of -- or the other strategy has not been

pursued and then the endgame is reached. So I think where to start, it's a great place to start, but it should not then exclude other strategies that then would bring to bear, you know, clinical experience in the civilian setting and promulgation of a market, you know, a business plan. It gets it off of -- potentially gets it off of the military's -- it flourishes in the civilian setting.

DR. KING: So I bleed Army green also. But like John, I also straddle the civilian world, and somebody's going to have to explain to me why, despite the fact that I bleed Army green, a soldier's life is more important than my son's, who is in a bad car wreck with his liver laceration. Why is that guy -- why is one population more important than the other? And why would we want to restrict a potentially lifesaving device to one population or the other? Tim is right. I mean, the research should be on the indication and identifying the right patients wherever they are.

DR. ASHAR: Yeah, you know -- let me -- oh. Go ahead.

DR. ELOFF: I would just like to take off my public health hat for a second and put on my contracting officer's hat and talk about the public investment. You know, so many of these things are developed with the support of the DoD, similar to programs that we have at FDA to develop new tools and, you know, really, any government agency has probably the best story or, of course, duty. And NASA really -- well, the investment is being made for -- to meet mission-critical needs, the return on the investment is when those things are put out to the general public. You know, where would

we be without Velcro? I'd be tying my son's shoes every day. And Tang, you know, wonderful things; Mylar and all those great things that come about from the space program, you know, I think that NASA got to put them first on their spacecraft, but moved eventually. So I agree, there shouldn't be an endgame for battlefield use only, but I wouldn't be necessarily disappointed if that's where it got first.

DR. ASHAR: I think Dr. Champion has been waiting patiently.

DR. CHAMPION: Thanks. It's been interesting listening to this debate. I would like to step back a little bit, and I think there's an opportunity here for the FDA to actually harness the up tempo that has developed as a result of efforts emanating largely from John when he was in the military and continued by many others. But there is a huge innovative horsepower out there being directed at hemorrhage control, particularly early hemorrhage control. And the kiss of death for that is going to be the classical approach to approval of devices or drugs or whatever.

And so what I would like to see the FDA consider is a premarket à la carte checklist of maybe, I can think of up to 20 items that are on there, which would be item specific. You would have to check off a certain number of those before market, and then there would be a conditional approval of the item, the drug, the device or so, which would require you to submit data on every use, which would have to be reported yearly and checked to the degree that if you sell a hundred of those and you reported uses on five, then

your conditional approval would be withdrawn.

So I think whether that's being a bit tough -- and I'm sure we'll hear tomorrow or later on today from the manufacturers that some FDA oversight, an à la carte approach, not a cookie cutter approach, and a binding obligation for postmarket data would be a combination worth considering. These are very complex issues and the big killer is time and money. And if we don't allow flexibility to address that, then this is going to die because there will be no business model for it in the next few years. H.L. Mencken up in Baltimore used to say for every complex problem there is a simple solution, and it's wrong. And I would just try to hold that thought as we continue the discussion.

DR. ASHAR: Great, thank you.

Does the panel have any comments on that?

DR. RASMUSSEN: It would seem like there may be room for -- I mean, or is there room for -- you know, Dr. Champion mentioned the complexity of this, and I think we've articulated it in the panel throughout the morning that there may be precedent for advisory panels that exist, that are federal, sort of -- either FDA, military or -- you know.

And because trauma research, trauma regulatory issues -- you know, I mentioned the word "strategy" two or three time, regulatory strategy, and certainly a failed strategy or a misdirected or misguided strategy is costly for time and money. And perhaps there would be room for

an advisory panel that existed -- and I know that there has been some discussion of that and led by some members in this room, Allison, perhaps included. But it starts to make more sense, so that the advisory panel could try to advise on regulatory strategies as they were being considered in the development of these products. And on that panel could be military and civilian trauma, you know, both, because they're inseparable, as we -- military and civilian. And they'll become more inseparable as combat operations wind down in Afghanistan.

DR. ASHAR: That's great. I think that underscores what Ben said in his talk, that this is a collaborative effort, and we have to have engagement by all interested parties to make something of this magnitude really meet all of our needs.

So did you have a question?

UNIDENTIFIED SPEAKER: I just had a quick statement, going back to the battlefield thing. I think the battlefield statement on an indication now is irrelevant because we tend to think of the battlefield as Afghanistan, Iraq, and the desert. Guy in uniform, got all this gear on. The battlefield is here now. It's a small world, and every one of you EMS directors, you're on the battlefield now. So that indication, you can -- it's irrelevant, so I think it can just go away.

DR. ASHAR: Yeah, excellent point.

DR. KING: Yeah, you can just go walk around after the Boston

Marathon last year and recognize that the battlefield is an omen.

DR. ELOFF: So I wanted to get back to the question of regulatory strategies for a moment and echo a comment that Amanda [sic] made earlier, that one of the CDRH strategic priorities for this year and next is to reexamine the pre- and postmarket balance evidence collection and analysis towards promoting innovation in medical devices. So we are looking for new ways and new methods, new data sources, so that we can get devices to market and also maintain the very high level of safety and effectiveness assurance that we already have, because the worst thing that we could do is get a faulty device on the market that does more harm than good and not have the data collection infrastructure in place to catch that and expose potentially thousands of patients to a device that not only doesn't save them but actively contributes to their injury.

DR. RASMUSSEN: This is where TQIP -- John, right?

DR. ELOFF: Yeah.

DR. RASMUSSEN: TQIP can play into that.

DR. ASHAR: Dr. Alcorta. Oh, I'm sorry.

DR. MARCOZZI: Can I make --

DR. ASHAR: Yes.

DR. MARCOZZI: Yeah, sure. So I think this is also timely for the FDA. We were at the critical care roundtable discussions with a lot of -- you know, some of the SME across the nation; at that meeting was our other

colleagues across government, which is the legislative branch. And currently the Congress is thinking about how FDA can start to think about and strategize more streamlining safety by working with other components, either civilian or other parts of government to make it more efficient. So this might be a time for FDA to actually raise its flag and go we might be able to do this and here's an idea, to promote to the Hill that we all embrace, collectively, both civilian, across government, that the Hill that embraces and makes law -- so this is a key time for FDA to have these discussions.

DR. ASHAR: Yes.

DR. HOLCOMB: A comment and two questions. The comment is especially on statistical analysis of these trauma data; we spend a lot of time with our statisticians and epidemiologists. Many methods are designed for cancer and heart disease because that's what's been funded over the years. And cancer and heart disease, if you have an intervention, then what you see is -- and it's effective. You see a separation over the next week, months, and years. And so the Kaplan-Meier curves start together and they separate.

It's very interesting, the trauma data, for the most part, especially in hemorrhage control. What you see is if you're going to see a separation, you see it in an hour or two or three. And then you don't see -- because people are either alive or dead at that point. And then what you see is fairly parallel lines. And almost every Kaplan-Meier on every trauma study

I've gone back and looked at over the last 20 years has almost exactly the same curve. These separations are very early and then parallel; they don't cross. And, yet, when you use analytic methods designed for cancer and heart disease, you end up with a study that has failed when, in fact, if you go back and look at it, there is a difference at 3 hours but not at 24 hours or 30 days. And that's because there's a competing risk of head injury.

It's a fascinating epidemiologic problem, great to sit around and have epidemiologic statistical discussions, you know, over a nice Bolla wine. But when it comes to approval, approval of products, it's an absolute killer. And so Howard talked about this a little bit. I want to be a little bit more explicit in my comments, and so that epidemiologic and statistical analysis is extremely important to these things.

And now my two questions. I didn't see any trauma registries on your list. Are you guys engaged in the trauma community with registry data?

DR. ELOFF: Actually, we are currently in talks to establish a relationship with the Joint Trauma System and are working to actually expand our portfolio not only to other trauma devices, but other medical device areas.

DR. HOLCOMB: It would be awesome to link in the American College of Surgeons trauma programs, the American Society of Anesthesiologists trauma programs, and the AABB has a registry as well.

They all need to be linked up, and you would have anesthesia, surgery, the emergency medicine databases, and then blood, right, which is so critical to everything we do in the sick patients. It would be a great opportunity.

And the last question is about EFIC. EFIC has been applied to Level III studies, you know. Phase III studies. And, see, what happens is you have this ethical conundrum of going from animal studies into Phase III studies without the opportunity to learn with Phase I and II. So can we use EFIC for Phase I and II so we can learn with smaller numbers of patients?

DR. PROHASKA: Well, the answer is yes.

DR. HOLCOMB: Perfect. Stop there.

(Laughter.)

DR. HOLCOMB: Done, period.

DR. PROHASKA: There's always the bottom of --

DR. HOLCOMB: Okay.

DR. PROHASKA: The answer is yes. You know, the regulations do not prohibit the use of exception from informed consent for Phase I or Phase II clinical trials. However, the same regulatory requirements about the prospect of direct benefit and all the other protections described in 50.24 would have to be satisfied.

DR. HOLCOMB: It's just a conundrum going from animals into a Phase III trial and you're prevented -- and I've read the regulation. There is nothing that prohibits, but it's kind of the culture and what has been done,

the unwritten rule. And we would like -- I think investigators like the opportunity to learn, as with any other drug/product that's out there, the lessons learned with Phase I and Phase II with smaller numbers of patients. And so when you talk about benefits and benefit, you actually would be able to apply those concepts, I think, to Phase I and Phase II studies before leaping into large Phase III studies.

DR. PROHASKA: I can see the benefit of doing that. However, like I said, it may be difficult with only preclinical information to show the prospective direct benefit. So I would recommend, if you were contemplating that, to talk with the review division early.

DR. HOLCOMB: Agree.

DR. ELOFF: Could I come back to your comments that came before you put me on the spot with questions? The first thing, I'd like to state the disclaimer. I'm not actually an epidemiologist; I'm an engineer. So, because of that, I like standardization of things. There was a discussion this morning about why doesn't FDA step in and force everybody to do the same data collection in their endpoints. And just a moment ago, Colonel Rasmussen mentioned that big data is not what we want; we want the right data, and we want that right data to be of high quality also, not only collecting the right things.

So I would say that in the collaboration sense, we do need to take a page out of the cardiovascular community's playbook. In the concept

paper it mentioned TIMI and GUSTO and things like that. Well, there's the academic research consortium which came up with the BARC endpoint, which can be used in clinical trials for FDA, which can be used in clinical trials for NIH, which can be used in registries, by the ACC, by STS, so on and so forth. And everybody knows what BARC is, you know, it's been published, it's been vetted by a multi-stakeholder, multi-disciplinary team. It's been vetted in -- it was developed with the Center for Devices, Center for Drugs. I think there were Biologics folks on the development team as well. That type of thing, in the trauma space, would go a really long distance towards being able to have a more easily done clinical trial both on the prospective stand-alone, but also to incorporate within registries and make them less burdensome and more easily understood by everybody.

You know, there was also a thread earlier on how do we standardize practice around the country or within each state. You know, the federal government doesn't have a magic wand or an infinite number of sticks by which we can beat people into compliance. We are really good or at least getting better at collaborating and working together and offering carrots to promote that collaboration and really show, okay, let's make a change, you know, let's investigate a change in New York and see what happens there. Okay, well, Ohio. That seemed to work really well in New York, why don't you guys bring up yours just, you know, as an example.

DR. ASHAR: I have a couple of people that are waiting for --

DR. ELOFF: Okay, sorry.

DR. ASHAR: They have some questions for the panel.

Sir, did you want to go ahead?

UNIDENTIFIED SPEAKER: Yes. We developed in a study agents and we agreed we take the aid, that the product should be tested for safety and efficacy properly. As a company, we could not face liability for dangerous product and we would never do it. Perhaps if they could make the trials, Phase II, Phase III a little bit shorter, reducing the number of patients, facilitating the process, but certainly safety and efficacy should be properly --

DR. ASHAR: Yeah, I'm sorry to hear that that kind of died on the vine, didn't it? But, you know, this is what this conference is hopefully going to address, and hopefully, we can develop some streaming data sources with this Joint Trauma System that was mentioned very early on in these panel discussions, you know, some sort of infrastructure that allows us to obtain some sort of data in a way that's not so burdensome on any individual company.

But that's going to take some time and so, you know, we talked somewhat about the difference between big data and the right data. And I'm wondering if the panel can comment on where the best bang is for the buck? I mean, it seems like there are a lot of registries out there; some meet some needs, others may meet different needs.

For what we're talking about here, the severely injured patient

that is bleeding and dying in the first hour, is there anything that we can leverage that exists today that could help us obtain data and fill this gap where we're trying to obtain clinical information in the premarket setting? I mean, in a limited way, you know, under IDE -- is there something that exists today, or is this something that would need to really be developed or a database revamped to achieve?

DR. RASMUSSEN: I mean, I'd be interested in -- you say it's a long ways away, and yet John outlined a study that will begin imminently using elements of the American College of Surgeons committee on trauma, TQIP, which is really a performance improvement registry, initially. But he's going to -- you know, we are funding that with collaboration with the NIH/NHLBI, and that will begin to enroll relatively soon, so not far away, and we may get insight into the ability to use TQIP, and I'm not an expert on that. So that's one. I mean, I think I'd be interested in John or other people who think TQIP might be something like that, that might be useful in that context.

We also have a national trauma research database that we are funding and beginning to -- or that has been funded and is beginning to be put together so that DoD research programs, projects in trauma will have common data elements entered into this NTDB that may be amenable to that, but, I mean, what do you think about TQIP, David or John or -- is that going to be -- is that something that can be morphed into something where we can get that sort of data as far as research goes?

DR. HOLCOMB: Well, the TQIP -- what most of these databases are missing, and to include our registry and our hospital, is hourly data. You know, blood pressure data, transfusion data on an hourly basis for the first three, four, five -- you know, 6 hours on an hourly basis. No standard performance improvement registry, national trauma, which gets another million patients a year. TQIP, which has a couple million patients entered right now, has hourly data for the first 6 hours, which is all of the data that we're showing. This is when all the action happens. So what we tried to do in this study is to meld 24/7 people that are out of the clinical milieu recording what goes on and then utilize the TQIP data, which is really good for ventilator days, multi-organ failure days, sepsis, and that sort of thing, later. Trying to balance the best of both of those.

DR. KING: Yeah, John very eloquently articulated where patients are dying and no current -- to my knowledge, no current database has enough granularity on the patient that dies in the first 5 minutes versus 10 minutes versus 20 minutes versus 1 hour, and it sounds like the crux of your question is getting not only at that, that's at the hospital. There's a whole arena of care that already took place long before that guy ever got there, and we certainly don't have minute-to-minute or even 5-minute or 10-minute to 10-minute granularity on what happened in the prehospital environment. It doesn't exist.

So TQIP is a very reasonable place to start, but I would propose

that there is not a very good existing solution, but to -- yeah, Howard's smiling over there. But he's right. So there is a solution. I suspect it's simpler than we think it is; we just haven't quite come up with it yet. But it's not simple; it's just simpler than we're making it out to be.

DR. RASMUSSEN: There are two existing elements that may be able to be adjuncts to TQIP and both -- you know, we've mentioned them and I can -- I think the JTS is online or viewing or they're listening; I've had some texts from them. And so, you know, Colonel Kirby Gross is the JTS director and there is a prehospital -- and they have implemented effectively now, over the last two or three years, their ability to get prehospital data in the military setting, so certainly looking at how those after-action reports are conducted, what the data is, and what that meaningful information that they're gleaning is potentially very important. That's one.

And the other is the Navy's Combat Trauma Registry, which exists as a part of NHRC in San Diego. You know, they also have had a prehospital-centric, sort of -- so there are some models out there. They're no longer, fortunately, gathering a lot of prehospital combat data on injured personnel as operations wind down, but there may be elements of that model that could sit next to or be learned from by the American College of Surgeons TQIP that may give us something. I'm not sure.

DR. KING: Yeah, that's exactly my point. I think we don't need to reinvent the wheel; we need to lean on existing resources and technology

and maybe draw them into this to help us answer the questions.

DR. ASHAR: Dr. Marcozzi, Dr. Holcomb, and then Dr. Champion. And I think we're starting to run out of time, so we'll conclude after Dr. Champion.

DR. MARCOZZI: Yeah, a tactical and a strategic discussion. First, I think, from a tactical standpoint. The problem with the prehospital care is that we don't have a very good means right now across either in the civilian sector and the military sector to collect minute-by-minute, hour-by-hour patient data collection. Show me the electronic health record for the prehospital system in DoD, and that's a systole.

I mean, right now it's done by charting, it's done by hand jamming it, but an electronic health record for the prehospital, show me the prehospital system for the civilian sector that's universal across every state. So there are some that have it, but it's not universal. So I think that one of the tactical things that we can start to work in is to develop better means to collect data and electronic data to health records so that we can roll it up to an epi standpoint.

The second is the strategic piece. And the strategic piece is, the civilian sector and the DoD both suffer from the same thing. You have a great civilian -- or at least Grade A evolving data collection system in NEMSIS, National Emergency Medical Systems Information System. So National EMS Information System, NEMSIS. Collection in, I think, 37 states. It then has no

linkage to outcomes. No linkage to outcomes; it's just an isolated data repository. DoD, in essence, kind of has the same thing.

FDA can help shape both of those markets, both the civilian sector and the military sector, and say this is what we need from an FDA standpoint to start to think about technology systems to provide better care both in the military and the civilian sector. FDA can be one of the pillars of which to help shape those two, to connect to data collection to outcomes, which is what we don't currently have.

DR. ASHAR: Dr. Holcomb.

DR. HOLCOMB: Just a comment on data. As we've looked at these registry studies, we've looked at prospective randomized studies, observational studies. The data that's missing is on the sickest patients, and every registered person knows this, so the data are not missing at random. And then you got to figure out how to handle the missing data in the sickest patients, which are the ones you're really interested in. Because when you go back to the charts, people aren't really worried about charting; they're interested in taking care of -- they fell off the chart later, and it's usually wrong. Multiple issues with data. I tell you, Dr. Marcozzi, what you just articulated may be the most important thing to come out of this meeting.

DR. ASHAR: And, Dr. Champion, you get the last word on this panel.

DR. CHAMPION: Just very quickly. DOT spends millions, tens of

millions, every year on databases, fatal -- the Fatal Accident Reporting System, FARS; the National Accident Sampling System; and I think they're also funding NEMSIS through NTSA. And so they've got decades of track records and gazillions of records that go back, you know. And talking to them, particularly with respect to the FARS database for prehospital deaths would, I think, be an essential starting point, among others.

DR. ALCORTA: If I may? The one other piece is, I think, where you're hearing from us is there is the National Health Information Exchange, which is really designed more for the primary care doc and seeing what meds they're on. And when they come to the emergency department, I can reach in very quickly and find out, you know, what their last set of prescriptions and their illnesses are. But the reality is, we're moving into an electronic arena, and these databases have got to interface, and they need to be readily available, not just for patient care, but for true long-term research and improvement of healthcare systems. And that's what I'm really hearing here. But, again, it's got to be the right pieces of information that we need, not just a lot more of things that are not so useful.

DR. ASHAR: Right, okay. And, Ben, I think you have 30 seconds. And I want to get everybody out so that we can stay on schedule.

DR. ELOFF: Use my 30 seconds, okay. I just wanted to say there are good registries and bad registries. The best registries are the ones that follow clinical care and collect that data, and even better than the best

registries are the ones that import it directly from high-quality EHRs. To Dr. Marcozzi's point, about connecting field care with outcome data, we've actually funded a registry at the University of Washington, a project looking at field-deployed AEDs, the ones hanging on the wall out there, connecting use of those through the EMS system, through the hospital to discharge outcome data. And we're looking to learn from that experience and see how we can incorporate that type of system in other areas as well. So we're working on exactly that type of investment right now.

DR. ASHAR: Okay, great. I think what we'll do is we'll reconvene in about 15 minutes. I have 2:40 right now, so that should be about 2:55.

All right, great. Thank you.

(Off the record.)

(On the record.)

MS. KUMAR: We are going to begin Session III. Session III is about assessing safety and effectiveness. And over the next hour and a half or so, we'd really like to hear from industry and have discussions with industry, with those stakeholders in the audience, to gain an understanding of the types of novel products that are being developed to meet the unmet needs that we've heard about today, and to understand their challenges both with the target patient populations that they've evaluated with their products, to hear about their regulatory strategies and some of the human

factors considerations that they've taken into account.

I'd like to introduce Lance Hopman, who is the Director of R&D at SAM Medical Products.

MR. HOPMAN: Thank you. So I'm going to go over one of the junctional tourniquets. This is probably a good place to start with industry, since this is already on the market. And as Dr. King mentioned, you know, I think the gap on junctional tourniquets, at least, is narrowing from a technology standpoint -- maybe. Certainly not from an implementation standpoint. Either way, I'm going to go over, sort of, a case study of how we got to market and where we are now.

So, first, a couple seconds on SAM Medical Products. We really focus on developing and manufacturing products for prehospital trauma. The company was founded about 30 years ago on the SAM Splint for extremity fractures, and that was the life blood for quite a while. We started an R&D initiative a few years ago and came out with the Chest Seal hemostatic dressing, a pelvic sling for reduction of pelvic fractures that I'll talk about a little bit later, and then our recent effort has been on junctional tourniquets.

As people have mentioned, this is for compressible but non-tourniquetable hemorrhage. So, really, circumferential pressure is not going to work in these areas where the torso meets the limbs. But a point of pressure might work, either if the pressure is applied on the injury site or proximal to that to compress the artery to occlusion.

So the background for us, anyway. The whole clinical need -- you know, this wasn't our idea. The military defined pretty well what the clinical need was and how to do it really. There's been a medic technique out there of using manual compression on any of these pressure points to achieve temporary hemorrhage control. So what the military really wanted was those -- that your arms can only hold out for so long or your fingers can only hold out for so long. So they put out an RFI for industry to turn this concept, you know, the clinical need and the method into something that's commercialized and mechanical.

So at the same time that they put out this RFI, we started to see a lot of literature out there that the primary cause of the need was the improvised explosive devices, and that there is a high incidence of pelvic fractures associated with those, which makes sense. There's a lot of force directed up into that area. So, if you have a high amputation or a wound that is higher than a tourniquet can reach, probably the pelvis saw a lot of force as well and had a fracture.

So it was a pretty simple idea for us to marry the existing pelvic binder that we have with something that could provide a pressure point, and that's the creation of the SAM Junctional Tourniquet. And on the upper left there, that's our original SAM sling pelvic binder. The whole concept behind it is that there's been a lot of work done to show that there's an upper limit safety-wise and a lower limit efficacy-wise of force that's need to reduce a

pelvic fracture. So this device has a mechanism that controls the force applied to that range.

We basically took the same thing but ruggedized it, I'd say militarized, for size and weight while keeping the same efficacy, and then adding a detachable pneumatic puck that inflates and provides that point of pressure with a detachable hand-pump. So it's a little bit versatile. You can put the point-of-pressure devices where you need, based on the anatomy of the patient, and potentially blow up multiple pucks with one hand-pump that cuts down on cube.

So the first indication for where you would apply this for junctional hemorrhage is in the inguinal area, compressing around the inguinal crease to cut off flow on the common femoral; and the second, the shoulder area, for junctional. There are a couple fittings that adapt this to the shoulder area and the target point. There is a pocket under the clavicle where the subclavian artery turns into the axillary artery, and it's probably the most proximal point that you can go for a bleed in the shoulder. You can go a little bit more distal, but this buys you a couple inches.

The regulatory strategy: So we have two 510(k)s on this. The first was inguinal area hemorrhage and pelvic fracture. And the predicates we used there were our SAM Pelvic Sling for the pelvic fracture reduction and then the CRoC, or Combat Ready Clamp. And the Combat Ready Clamp really paved the way, as far as junctional tourniquets go, both from a technology

and an implementation standpoint as well as a regulatory standpoint. So, when they got the inguinal hemorrhage cleared, we used them as a predicate for that. When they got a second 510(k) for axilla hemorrhage, we used them as a predicate as well for that.

And I think it's been gone over before, but the devices fall under DXC product code, which is vascular clamp, Class II prescription devices and not really -- you know, the predicates ahead of the Combat Ready Clamp were vascular access devices, cath labs, things like that, so not really tourniquet devices, but things that were just point-of-pressure devices. And it's interesting to note here, too, that in the EU for CE marking, these devices are just tourniquets, so they're Class I. They're Class I devices over there.

I'll go over a little bit of the clearance testing we did for submission, and then I'll go over some of the testing that was done post market introduction. So this is all for submission: safety testing, standard biocompatibility, robustness, over-accelerated conditions for shelf life, and then over the 4-hour use period that's been defined by FDA as well as military -- not FDA-required testing, but military-required testing such as MIL-STD-810G.

Performance: The Institute of Surgical Research, the Army Institute of Surgical Research at Fort Sam, has a manikin model that simulates human tissue and vasculature, and you can make it bleed and show that these point-of-pressure devices can occlude the pipe.

Human cadaver: That is what's pictured up here in the diagram. Basically, it's a perfused, fresh, un-embalmed human cadaver that you hook a pump up to one side of the vasculature and then open up a sentinel bleed. And you can show if you apply pressure at any point in between on the vasculature and are able to occlude it. Then the blood from the sentinel bleed site will stop.

And that's really it for the performance testing for submission. And I put "Why no swine or live animals?" And there are really two reasons, and the first is anatomical differences. You know, swine are different enough that the thinking was that a human cadaver would be better. And the second is that this is really a simple mechanism of action. It's basically plumbing, and if you provide enough pressure on a pipe to collapse it, then you're going to have blood flow. It's not quite as complex as some of the chemistry that might go on with a hemostatic dressing or some of the things that we're going to be hearing about next from some of the other companies.

So postmarket testing: We sponsored one at Oregon Health Sciences University to look at -- 10 persons volunteered just to look at occlusion of the femoral artery via Doppler, and this has just been published in the *Journal of Vascular Surgery*. And the second part of that, though, was looking at residual limb perfusion in the muscles through capillaries or collateral flow. And that has implications to long-term limb survivability on remote or extended missions.

Secondly, the military: The international militaries really are collaborating on doing a bunch of comparative studies between -- there are four junctional devices on the market. And this goes for military or civilian, too. The military or EMS medical director is not going to take a company-sponsored study at face value, and they're not going to take an FDA clearance at face value and say, oh, it must work; we're going to put it into the field.

They're going to want to do their own testing, and if it works and if the best device is reasonable, then they will field it. So this is really -- they're going to try to narrow it down to one or a couple devices and start fielding them mass scale. Right now, the only uses out there are probably special operations forces, and that's the only way that we're going to get case reports directly in.

So this is one that just got published from an Afghani national. And that's what it's all about, but we'd like to see the devices fielded.

And I will end with a couple challenges that we faced and are still facing really. One of the main ones is that the user at the point of injury is not a doctor. You know, a medical director from the military side or civilian is putting the device -- and the decision tree of when to use it and how and why -- in the hands of somebody that is, I'd say, variably skilled. But you can have pretty well skilled or hardly skilled at all first responders to these injuries.

So the first part of the design is, they have to be physically

simple, intuitive, and familiar. And that's what we tried to do with this, is if a medic, an EMT-B or a combat medic knows blood pressure cuff and he knows a belt pelvic binder, he ought to be able to figure out this device pretty well. And we went through multiple iterations along the way of talking with the combat medics or with the EMTs to say, okay, how could this go wrong, and then come back with three different solutions and then what's the best one out of that.

A second one here. Directions, indications, and contraindications must minimize the decision tree. And as an example of that, one of the four devices is cleared for making the pressure point on the belly button, basically where you can compress the abdominal aorta above the bifurcation of the iliac arteries. And so for our device, with a pretty simple design tweak, we could make it work for that, and we could do a study and we could get a clearance for that indication.

But a lot of the directors and military decision makers are saying okay, but then that comes along with contraindications. So you're asking a medic that is not all that skilled to make a decision that would usually be done by a physician. You know, does the risk of using this with a contraindication -- like is a person pregnant or do we have penetrating trauma, that kind of thing -- versus where are you going to apply it on the body. So it sort of muddies the waters, and we've tried to keep it pretty simple. That's still a debate that's ongoing internally for us.

The second part here, or the last point, is translating military requirements to a civilian population. And the nice thing about having this from the military in the first place is that they're very specific in the requirements. So you have a specific injury, how to treat it. Basically, you know, we're just giving the means to treat it. And then what the patient demographic is, too. You know, it's really fairly homogeneous.

And at the start, we were pretty okay with that because we thought this was pretty much a military only market for some of the reasons that Dr. Alcorta went through. But as time is going on, with the Boston Marathon bombing and greater awareness of these mass casualty incidents, we started to think that that might not be completely the case. So you have a non-homogeneous population at that point. You have pediatric, geriatric, bariatric.

So the first thing to address this is that the device has to be flexible. Like I said, the point-of-pressure devices are removable, adjustable so that regardless of the anatomy of the patient, you're going to have a chance anyway of this working. And then the second aspect of that is directions of use being extremely clear, training being extensive. On the military side, that's a little bit easier, but with the fracture EMS market, it takes a lot of work for a company to reach everybody that they need to.

And I'll leave at that. Thank you.

(Applause.)

MS. KUMAR: Thank you.

Our next speaker will be Mr. David Spencer. Mr. Spencer is the co-founder and CEO of Pryor Medical Devices - The REBOA Company.

MR. SPENCER: Always go out for lunch and always make sure, when you give a briefing, that you sit in a puddle of water during lunch, which is what I did. So that's good to know. Those acrylic chairs outside actually hold water, and if you sit in them, they're wet.

Thank you all for letting me be here. I really am learning more than I am contributing, but I did and do appreciate a chance to get to talk about industry.

In Texas we have a saying that you have to be careful because some of those cowboys are all hat and no cattle. And for me to be up talking about our company, I'm a little worried about that because we're very early in the process. And so this is actually the first time I've spoken publicly about what we're doing because we're not out in the market yet, and I don't want to be that guy who's waving his hat around but doesn't have cattle. So bear with me if I don't talk a whole lot about our product; I really didn't want to make this a sales pitch. I did want to contribute a couple of extra thoughts, though.

So before I do that, though, just from a show of hands -- because I was trying to get a feel for the audience, if you'll bear with me. So how many of you are physicians? Just raise your hand. Physicians or other

clinicians. Throw that up there, okay.

So researchers? You can answer more than once, it's okay.

Industry? Excellent.

Entrepreneurs? Good.

Investors? Venture capitalists? Excellent, there's a couple of us. The venture capitalist secret handshake can be used later.

(Laughter.)

MR. SPENCER: Okay. So a quick background for me. I'm a little bit of a strange duck. I'm an entrepreneur at heart. I actually came out of the software business and then was fortunate in having sold some of my companies and became post-economic, and then was doing some public service for the state and was asked to run a venture fund and then did venture capital for a couple, three years, and have been an investor for 14 or 15 years now. And so I enjoy that, but it's not really my passion, and I've kind of come back to my entrepreneurial roots. But I made a deep error, which is, I decided that I would try and figure out medical devices, having absolutely no background in that. And the main reason is I live in San Antonio, Texas and that's where a large portion of the medical research is done, right in my backyard. And before I go on, I do want to just thank the military.

I'm telling you, just from watching this morning, Allison, I would have changed my entire briefing to being one talking about the importance and need for the Congressionally Directed Medical Research Program, and I

would make this a big sales pitch on that. And I do want to come back and talk to that. But you did ask me to talk a little bit about products. And then, luckily, I never let my lack of facts or knowledge get in the way of my opinions, so I might share a few of those, too.

Before I go anywhere, I've been taught to talk about clinical need. You've seen this reference. It struck me that almost half of those researchers are actually in this room right now, which is an amazing statement. And so I'm so grateful.

By the way, when you're a non-techie, you steal slides from other people. This is an important one that leads into where we, as a company, are focused. I do want to talk about this one, this specific paper by Demetriades. It's not been referenced, but everybody is likely to have seen similar stuff relative to the timing of trauma-related death.

And so as you see there, still the largest number of deaths comes from central nervous system stuff. But if you look, really, when you talk about preventable death, that's a hemorrhage, and that's happening within the first 24 hours certainly, but really, as speaker after speaker has talked about, really in the first few hours. And that's really where our company has been focused, so I won't go into REBOA.

By the way, if you ever deal with the military or, I'm now learning, with the FDA, you have to have an acronym. So that's good, we've got ours: REBOA. Although, in a previous life, I did some work for the

military, and we had acronyms that actually were nested acronyms. When you expanded them they had other acronyms inside of them. But we're going to stick with one, which is this: Resuscitative Endovascular Balloon Occlusion of the Aorta. And some of the top clinicians in the world that are sitting in this room are doing this procedure even as we speak -- well, not even as we speak, but their colleagues are, I hope. But do we have a trauma-specific catheter? And that's really where our focus has been, as a company.

So just quickly running down. We have tried very diligently to use the KISS principle, which is to keep it very simple. And so the balloons that are out there have traditionally been used by interventional radiologists or cardiologists and not for a trauma setting, and so an IR lab is a very different place than an ER.

And so some of the very specific requests from the trauma community have to do with being percutaneous, first of all, so that you don't have to have a surgical repair when you take the catheter out -- and that's less than 7 French in outer diameter -- and fluoroscopy-free for placement and speed. And that's really this one-pass concept where, instead of doing some of the more traditional vascular procedures where you're doing wire transfers and dilators to get to an ever-bigger bore so that you can run interesting stuff up into the vasculature, can you do it in one pass? And then of particular interest, if you're occluding the aorta, is pressure monitoring and having that north of or distal from the operator, proximal to the heart and

hopefully in between where the heart is and the hole is.

So what I tell my mom -- and she's always my -- if my mom can understand it, then that's probably pretty good for the general population. The whole idea here, as you've seen from other speakers, is to just stop the bleeding except for your heart and your lungs and your brain. If you've got something wrong with those, you're in bad shape anyways.

So that's our device. Where are we in the process? If you saw Dr. Eloff's circle, we're kind of just on the back end of coming out of the circle, so we are in a pre-submission standing.

I will tell you that the FDA, in particular, has been very forward leaning and engaging with our company. And so I can say I was reminded of -- I come from San Antonio, and they won the NBA championship recently. And not that anybody remembers that except for those of us down there. But they were working on the team, and I was talking about being involved with a championship team, and what's the big deal? Because yeah, we won. And then you think about folks who have gone their entire career in the NBA and never even made the playoffs. So I kind of feel like that rookie a little bit because I've stumbled into this at a very interesting time. I do want to talk a little bit about that.

You did ask me to go through some of the specifics, but I would just point out a few that are directly related to us and then maybe pass on some of the others. There's been a great discussion around trauma, being in

trauma, whether that's Dr. Holcomb's civilian or military -- he had a great slide on that -- and patient demographics.

For us in particular, one of the interesting things that will play out, I think, relative to this technique is vascular access. And there is probably a marked difference between the folks at the Boston Marathon who had traumatic limb amputation in the field and how you get vascular access for that person versus a car crash victim who maybe has a fractured pelvis but doesn't have both legs blown off. So that's something that's of interest to us that is really secondary to our device.

But I want to spend the remainder of my little bit of time talking about that last bullet. Funding: For human factors, I think that the whole idea behind the low weight and low cube that the military is very interested, and which we're interested, in just makes a ton of sense for the civilian market too.

The other day I was riding in the car with my teenager, and we stopped at Subway, and he got a bag of potato chips and he opened it, and he said, look, dad, I got a bag of air. And it was a big bag of chips full of air, and then there's this many chips in it. So I'm not sure the entire commercial community believes like I do in low weight and cube because sometimes you want to puff up what you got. But that goes back to the all hat and no cattle thing. For us, it's absolutely about durable packaging, easy open, low weight, low cube.

But I do want to talk about funding in particular, because I'm genuinely curious about whether or not we're missing an opportunity. And so on my last slide, I did want to pontificate a little bit, if you'd indulge me on an outsider's view of some kind of headwinds and tailwinds for where this group is. And so clearly this is a great, great top group of thought leaders, and I really use a word on here that comes to mind as I sat through the morning, which was this relentless focus on mission.

And I confess freely, I am an Army brat. My dad was a hospital administrator in the Army. My sister was a physician in the military, and my father-in-law was a physician in the military. They're both retired now. I grew up around military hospitals, and secretly I'm a biomedical engineer.

But mission is, really, no one should bleed to death. I mean, if you're going to die, die for some other reasons, but don't bleed to death. And that's all I've been hearing today from a very impressive group of thought leaders and clinicians across the military. Clearly, the FDA is leaning into this issue by virtue of the fact that we're having this meeting, but I also think there's some industry folks that have demonstrated an interest in this.

But that's really where I want to challenge this group and ask a couple of questions. And the question is really this: I discovered that there is a fairly robust commercialization infrastructure for medical devices in the country, and they are not in this room, and I question that, and I wonder why that is. It's been a question that has gone back to me really five years ago

when I first met the folks at MRMC and I saw some of the fascinating innovation the military was doing relative to lessons learned in war, Dr. Cardin. And I thought, well, wait a minute. I know and hang out with a lot of folks that do medical device development, and why aren't they here? And what might we gain if we were to engage with that community?

So I have a mentor; his name is Jack Gill. Some of you may know Dr. Jack Gill. He teaches at Harvard Medical School, he teaches at Stanford, he teaches at -- he also teaches at Rice because he retired to Texas and is building a lake house on Lake Jackson for his grandkids. But he spent 30-plus years in the medical device venture capital space with a company called Vanguard, and they created over 1.5 billion -- billion with a B -- dollars in wealth doing nothing but medical devices.

And five years ago I talked to Jack, who is a friend and a mentor and worked with me on this venture fund for the state, and I said to Jack, "Hey, I'm thinking about going and doing medical devices." And this is what he said to me; he said, "Don't do it." And I thought, you know, "I know I'm an idiot, but I might be able to figure it out eventually." And he said, "I'm not talking about you; I'm talking about why would you do medical devices?" And I said, "It fascinates me. My way of giving back a little bit." He said, "Don't do it. And the reason you shouldn't do it is because the big money is somewhere else. It's in Pinterest, it's in Google, it's in other places. And then in medical devices you may get a single or a double, but you're never going to get a

home run. And even if you put a bunch of your own money into these things" -- which I have -- "there may not be money upstream to finish it out."

And so dutifully I went on and ignored his advice and did this, but it's likely that it's because I'm at a point in life where I consider risking some stuff, that if it goes south, then that might be my philanthropic effort as opposed to my purely financial effort.

And I want to challenge this community to think about this because it comes really down to the bottom, which is, is trauma going to demand the dollars? Is there going to be this ice bucket challenge -- which I saw another one just this morning and where folks were doing this for ALS and they raised $99. Who is the trauma ice bucket challenge? Is there a market, not just because a lot of people die from trauma, but because it's a compelling marketplace? And I would encourage, as we expand this discussion, that we think about engaging with folks that are out there that build medical devices in other areas and how we might engage them, because it might not happen otherwise.

And I'll end with this thought, which is back to my original comment, which is thank you to Congress and the American people. But more importantly, thank you to the military folks, now led by Colonel Todd Rasmussen, but others like Sylvain Cardin, Anthony Pusateri, and folks that are doing the work down at the ISR, like Mike Dubick and Heather Pidcoke and others. Because I really have a sense that if this is going to happen, it's

going to have to happen with the military leading the way, not just from a thought leadership perspective but from a funding perspective, until we have some examples, like here, that show that this will work and that there's a market on the back end of this.

So I look forward to your questions later and thank you for letting me go over a little bit on time.

(Applause.)

MS. KUMAR: Thank you.

I would now like to invite Dr. George Falus and Dr. Grant Bochicchio of Biomedica to come up and give their presentation.

DR. FALUS: Come, we're a duo.

Biomedica is a company based at UMBC Biotech Center in Baltimore. Our leading technology is a biologic device for noncompressible -- intracavitary hemostasis. In 2007, we were responding to an Army solicitation to develop an intracavitary noncompressible hemostatic agent. We proposed to develop an expandable foam carrying a fibrin hemostat that could be injected into the cavity. The idea had been proposed by Dr. Holcomb, who suggested to use either physically modified polymers, like chitosan, that could be delivered through a gas pressure canister. It looked like a simple and straightforward idea but, in fact, it was not.

Our first intent was to create a system of two components, one which would be a compression scaffold at a pH 3.5 containing fibrinogen that

would be mixed with a cross-linking part at pH 8.2 containing thrombin. The mix of the solutions would produce a gel which will release CO_2 and would create a foam that would expand the hemostat. It did not work because the parts interact with each other and the pH's were not compatible.

So the next step was to work for years, first to develop a new fibrin technology, what we call an advanced fibrin technology, that will be compatible with pH, that will polymerize faster and stronger. And we came out with a four-part solution: two composing the compressive gel, which was gelatin based with cross-linking agents, and two parts that composed the fibrin polymer -- by this gel. It was fibrin monomer solution that, when neutralized with a buffer, would turn into a polymer.

The standard way to make a fibrin sealant was to mix thrombin and fibrinogen and antifibrinolytics and preservative to create a cross-linked polymer. Unlike the standard way, we used the idea of dissolving fibrin in an acidic solution at pH 3.4, which would be neutralized by a buffer and then cross-linked by calcium independent transglutaminase that would cross-link two or three alpha chain, creating a strong polymer. Therefore, our technology avoided the initial steps of creating a fibrin polymer, starting from a fibrin monomer that finally turns into fibrin clot when crushed.

For example, if you mix fibrinogen with thrombin at a concentration of 25 mg/mL, the clotting time is 37 seconds. Reported administration of that monomer neutralized by a buffer was between 5 and 8

seconds, which is very important to prevent the hemostat to be carried away by the flow of blood.

With the help of Dr. Leonard McFelt (ph.), which is one of the pioneers in fibrinogen chemistry, we developed this new fibrin technology and we improved the way of creating a compressive gel. And, fortunately, the pH -- no, I'm sorry about that. And then we also created a way of polymerizing two of the fibrin chains to make it a very strong clot. We ended up with a combination product that was a biologic and an applicator device. The foam that produced expands 400%, compressing the cavity. It has a high internal energy and was able to maintain the fibrin in place and form a clot. The delivery method could be -- the product could be delivered outside the operating room, and most important, it could be tested in human trials, conforming a regulatory path with consent. As we tested one formulation, the substance changed, as well as the application device.

The system is a four-part system in which two parts form a compressive gel and the two other parts form a fibrin clot. This technology that's not contained in this final form -- thrombin, preservative, or antifibrinolytics. It polymerizes extremely fast and at a very reduced cost of manufacturing. The solution does not degrade because it is stored partly in acid solution, and that monomer can be formulated to form a gel, a patch, or a spray for many surgical indications. We call this a clot technology, which is patented. It is stronger, faster, cheaper, and purer than any fibrin sealant.

And Dr. Bochicchio has developed several protocols and models to test the product, mimicking a bullet wound or an explosive device or for use in the operating room.

DR. BOCHICCHIO: Thank you. My name is Dr. Bochicchio from Washington University, and I was going to race through a video.

(Video played.)

DR. BOCHICCHIO: One of the challenges is, most of my colleagues are here from the ISR. The initial thought was we would use a clamp to test the wounds. But for noncompressible, I usually create a laparoscopic model. For purposes of this demonstration, we're actually going to show you the open model so that you can see that this is something that we can actually do laparoscopically through some ports so that we don't actually have to have an open cavity.

So what we really do is create a severe Grade 5 non-survivable injury with a drill, and just like in the model described by my colleagues here from the ISR, we do a front and a back overlapping injury which is lethal to the animal with a preoperative splenectomy, and we make it the hypotensive model with the hypotensive resuscitation model.

So after we do that -- and, again, for demonstration purposes, we create a closed cavity where we inject the foam into the abdomen, and we close the belly with abdominal clamps, simulating a closed cavity model. And one of the things that is clear that we need is something that's going to

lead to survival to get these soldiers far forward, at least: survival 68 minutes to 3 hours. And so this is what it looks like after 60 minutes in an animal with a lethal hemorrhage, where you can kind of see the foam amalgamated within the animal and having hemostasis.

(Video ended.)

DR. BOCHICCHIO: So that was one thing to say, in this area where patients are dying, where can we utilize this technology? And it actually has to work in these patients or soldiers who are dying. And so this is truly like the lethal model where, if you're going to use a foam or a noncompressible technology, it has to work; and that is why we developed that model.

We looked at regulatory development, and we did all of the testing, looking at biocompatibility, intra-body testing, evidence of thromboembolism. And as you can kind of see here, that all the testing in preparation for the Phase I trial demonstrated that this product is safe or similar to the fibrin sealants that you see out there on the market today, like EVICEL or TISSEEL.

Looking at adverse events, this was a comparative trial, head to head against EVICEL, against something that's been approved on the market since, I believe, 1998. In this animal survival trial, there was no difference in adhesions, inflammatory response, embolism, edema, or postoperative hematomas in this animal trial of eight animals.

When you think of advantages, you're talking about not as many sutures in providing a foam. I think the other big thing is, how can we utilize this in a civilian setting? Foam technology that if you spray in there, that can be resolved in suction, has to have a domestic indication. So, if you think about what domestic indications would be, you have to think about laparoscopic surgery, like in an event where you're doing a laparoscopic nephrectomy. Or a partial nephrectomy is a key area. You think about postpartum hemorrhage, anywhere you can't really get your hands into in the laparoscopic world.

And in addition to being a trauma surgeon, I do a lot of advanced MIS, and so this is something, when you're doing a laparoscopic left hemicolectomy and you ding the spleen, you could potentially throw foam up there. Or if you're doing a partial nephrectomy, you could potentially throw foam after you do your partial nephrectomy, potentially not even using clamps. So it should decrease your OR time as well, you know, facilitating hemostasis.

(Video played.)

DR. BOCHICCHIO: This is an example of a video looking at a partial nephrectomy, something that's done at Washington University probably a half a dozen times per week for renal cell carcinoma. When you do this laparoscopic, they do clamping. And usually after the clamping, you're there for probably 20 minutes or 30 minutes trying to throw sutures.

You're trying to use any type of advanced hemostatic product that you can find. And if all you needed to do was push a foam on there that would cause hemostasis and wait for about 10 minutes, then that's all you would really need to do. And you kind of see here that glowing area is just the fibrin clot that's present on top of the kidney there, which is basically showing the fibrin clot over hemostasis on that kidney.

(Video ended.)

DR. BOCHICCHIO: So, again, there could be a potential domestic indication for this type of technology in addition to the battlefield.

I'll briefly go quickly through some of the data. There has been a lot of data on ClotFoam. If you look at this, this is a non-GLP study on utilizing a non-lethal trauma model. Rather than doing a Grade 5, we would ratchet it down to a Grade 3, where we do the liver drill with a Grade 3 rather than a Grade 5. And you can see that the hemostasis is almost 100% in the ClotFoam arm with 100% survival, as compared to the control arm.

When you look at blood pressure in treated versus control subjects, you can see, in the ClotFoam arm, that the animals tended to maintain normal blood pressure versus in the control, they were not able to. And when you look at the lethal model, again, most of the controls died very quickly as compared to the treated arm with ClotFoam.

Other GLP: We looked at not only the liver, we looked at kidney, spleen, and multiple organ injuries where we would actually cut the

spleen in half, cut the kidney in half, and potentially cut some of the gastric arteries, simulating a multi-trauma. And you can kind of see that in this, that in the ClotFoam arms, that we were able to obtain hemostasis and survival in most of the animals as compared to the controls, where very few of the animals were able to survive in the comparative arms.

In terms of the GLP studies, this was again ClotFoam used with no compression, and you can kind of see -- again, looking at liver injuries, you'll see that ClotFoam was 100% effective at 2 minutes, 5 minutes, and at 10 minutes compared to the other products, including gel foam and EVICEL, which really did not obtain hemostasis until -- a few of them were able to eventually obtain hemostasis at 10 minutes. But as you went down to the kidney and spleen, again, ClotFoam demonstrated more efficacy compared to the control arms in this GLP study.

So going back to the regulatory path, I'll hand it back to Dr. Falus.

DR. FALUS: I'm going to finish from a regulatory point of view. R&D had extensive -- conducted safety studies by my colleague here -- pharmacodynamics. We are now in a Phase I trial that is in a university that will be followed by a Phase II trial as an adjunct to hemostasis and followed by a Phase IIb trial as a primary treatment. This is the regulatory path that we had agreed with FDA.

The next challenge: Our future challenge is to modify our

application device to make it non-reusable in the battlefield and -- this slide is not here anymore. I know what happened. The product is being developed also as a gel, a patch, a band-aid for many different end uses.

Our technology has been funded by TEDCO; Maryland, the University of Maryland; the U.S. Army Medical Research and Materiel Command; the National Heart, Lung and Blood Institute; and a small grant from DARPA.

Thank you.

(Applause.)

MS. KUMAR: Our next speaker will be Dr. Upma Sharma, who is leading the product development efforts for Arsenal Medical's novel foam system.

DR. SHARMA: Great. Thank you, everybody, for hanging in there. I know it's been a long but great session today. And I really want to thank the organizers of today's session. In particular, I know that a lot of work went into this session, and I think having all of the stakeholders in the room has been hugely valuable. So thanks to FDA for putting this together.

There has been a couple of mentions of our product today, and I just wanted to give a pretty high-level description of the product. In tomorrow's session, Thinking Outside of the Box, we'll go through some more of our animal data and some of the studies I describe here in more detail. So I'll be keeping it pretty high level here.

A quick slide on Arsenal and who we are as a company. We're a med device startup company. We're probably about 23 employees currently, so a pretty small company. We have products that are venture capital funded, and the product I'll describe here today, which has been predominantly funded by the DoD. And we really see our strength as developing products that are biomaterials focused. And hopefully you'll see that in the product I show today.

So our first experience with trauma came from a response to a DARPA program, a broad agency announcement in 2009, and the request was really to deal with the problem that a lot of folks have described this morning in great detail, and that was noncompressible abdominal hemorrhage. And the idea here was to have a product that would achieve hemostasis quickly, maintain that -- and specifically in the BA was called out for a 3-hour period; to be simple enough to be administered by an advanced medic, so that means in a far-forward environment not require identification of where the wounds were; ease of removal at surgery was called out; and then compatibility with field conditions as well.

So these were sort some of the initial requirements, and some of these have morphed over time, as you can imagine, through the development process. But this is really what started our interest in development of these products.

So described at a high level here, the device is a self-expanding

foam, a little bit different than the device we just saw in the mode of action. Our mode of action is focused on the pressure only, so there is no hemostatic agent within this foam. It's a two-part liquid system that's injected into the body, and the mixing of the two components triggers a chemical reaction that pushes the material throughout the cavity. So, again, it doesn't require any information of where the wounds necessarily are.

The delivery nozzle has been designed to be similar to a laparoscopic trocar with similar dimensions so that you can use standard access techniques to place the device into the cavity. And, again, as I mentioned, the mode of action here is really compression based. And then, again, it's a temporary device, so really providing a bridge to definitive surgery where the idea is for the device to be removed.

And we show a video here in the next slide that sort of illustrates this concept. It's a little bit cheesy, but it gives you a better sense of the concept here.

(Video played.)

DR. SHARMA: So a lot of people, when they see this concept, think of the Fix-A-Flat or they ask, well, can I go to Home Depot and buy foam insulation for my home? And when we first started this process, I will admit that we did go to Home Depot and we bought some products and we tried it out. And it turns out there's a lot of toxicity reasons you don't want to do that, as would be expected, but also that the engineering of a foam to

actually solve this problem is quite complex. And we've described it previously in some of the conferences. In total, to get a foam that actually works in these kinds of injuries, we've developed 1,300 different foams to really understand all the parameters to be able to optimize this problem.

It's not just the foam part. Thinking about being able to develop this and deploy this in a prehospital environment, whether that be the civilian side or the military side, requires a robust delivery system as well. In some of our early work, we used large delivery systems with big CO_2 tanks. Obviously, that's not really a field-able design, so we have developed a field-able system. I don't have one here today, but it really was developed with a lot of input from medics with the intent of being very easy to use, simple to use. And if you look at it again, it looks like a caulking gun, something you could buy at Home Depot, and that intuitiveness provided the simplicity that medics wanted and specifically in the military, on the military side, not requiring power, not requiring CO_2, being a very mechanically activated device.

The intended use of our device -- and we've been fortunate to have great medical advisors: Dr. King, who is here; Dr. Holcomb, who is here. One of the things we've talked a lot about within our medical advisory board meetings is who are the appropriate people to be using this device. And this is something that we discuss, I would say, almost ad nauseam for all of the reasons we've talked about today. You know, we really want to make sure

the appropriate users have the device.

The intended use is for very sick patients, patients who are in Class III or IV hemorrhagic shock, where they need a bridge to get to definitive surgery, whether that's in the military, whether that's in the civilian side, in a rural environment, whether that's in a Level 1 facility where there's not enough time to get to the OR. In all of those cases where you have very sick patients who have few options, this is where we see the device having a great benefit. And, again, it's a temporary device. It goes in. It provides a reduction of bleeding with the intent to just getting that patient to the surgeon, as Dr. King talked about earlier today.

We don't see this device being used by everyone. It's going to require a fair amount of training, and it's not just training on the device -- I think the device is quite simple to use -- but training in knowing who the appropriate patients are, training in the diagnosis and really doing that in a robust way. And I think a lot of that is also selecting the appropriate users, to start. So we don't see this as something a basic paramedic is going to be -- going to be used. Somebody who is paramedic level or higher -- sorry -- not a basic EMT, but somebody who is paramedic level or higher, somebody who has the skills to intubate a patient, to place chest tubes. Those are the type of skill sets that the users who use this device need to have.

Quickly, I will go through some of our performance data again at a very high level. And we'll describe this again in more detail tomorrow.

On the bench, we have done over 2,000 deployments of this material to really understand the reproducibility, reliability, the chemistry; a lot of work just to understand the methods, et cetera, to understand really what drives performance of the material.

We've coupled that with an enormous amount of swine work done in conjunction with Dr. King at Mass General Hospital. To date, we've looked at over 600 swine to really look at the safety and effectiveness of this device. And I say often, that if you have a pig with noncompressible abdominal hemorrhage, we know how to treat that animal right now.

And then I think one of the big questions we've talked about here today is making the bridge from animals into humans. And I think the advisors all felt like we had a very robust package of safety and effectiveness, but it was still a big leap to go from that to humans. And so what we decided to do was a study in recently deceased human subjects, and this really enabled us to test the device in more representative human anatomy. And I'll talk about this in a little more detail in two slides.

A little bit more detail on the animal testing. So I said we've used over 600 animals. This gives you a sense of where we used those animals. It took us about 60 animals across 16 different formulations to down-select to select the appropriate formulation. And Colonel Rasmussen talked about the concept of sort of empirical engineering, empiricism. That's really the concept we used here. It was a very iterative process. If something

looked like it didn't work, we quickly abandoned it and tried to iterate quickly to get to the right formulation.

Once we had that, we completed over 400 trials in a lethal liver injury model. This is a model that we created. And one of my team members, Adam Rago, will describe this process in more detail tomorrow. But, in short, we created models that were closed cavity models of extreme bleeding to really try to simulate what we see on the clinical scenario.

This is a venous bleeding model, and in this model we've tested a number of scenarios. We've tested sort of the baseline conditions, we've tested high and low doses, we've tested what happens if you have a diaphragm injury, what happens if you have a bullet hole injury. So you can imagine, there are a number of scenarios and we've been able -- a number of questions that have come up from the advisors, over time, and we've tested a lot of those in this animal model.

One of the other questions that came up after we had done a lot of this work was well, venous bleeding is one thing. What about arterial bleeding? So we developed a second model, an iliac injury model, which was arterial bleeding where we also tested the material. And in both of these models, what we've shown is, without any treatment, the animals will die in 20 to 30 minutes. Almost across the board, you see maybe 10% survival after 20 to 30 minutes. With the product you can get 70 to 80% survival out to 3 hours. Close to 100% survival -- 90 to 100% survival for the first hour. So a

very dramatic difference with the treatment versus no treatment in these models.

And then, finally, one of the things the advisors also emphasized to us is, well, it's great that we're saving animals acutely, but you can't turn a fast death into a slow death, and so really look, over time, what happens and are there complications that arise that you're not going to be able to see in the short 3-hour experiments.

So we did another set of studies in a non-lethal spleen injury model, where we placed the foam in animals, placed the foam for 3 hours, pulled out the foam, repaired the injury, and then survive the animals for 28 days and then also for 98 days, again to show that there were no long-term complications compared to a control arm.

And in addition to all of those tests, we've done ISO 10993 testing to establish biocompatibility. We looked at leachables and toxicity also, because this is an in situ form in chemistry.

So, in summary, I've talked a lot about some of these studies. In the liver injury, we looked at a range of doses, and with all doses we do see a survival benefit, and that survival benefit increases with increasing dose. In the iliac model, we looked at a subset of these doses, and we saw that, again, there's a survival benefit relative to the control arm. And then the spleen model demonstrated long-term viability of the foam treatment.

If you're interested, we're going to talk about this in more

detail tomorrow. We've also extensively published this work, so there are about six peer-reviewed publications out on this work, and the references are here and they're also on our website. So, if you're interested there, you can find more publications.

And as I said, going from this body of swine data, I think, made us feel pretty good about safety and efficacy, but there's still a big leap going from swine to humans. And so one of the things that we conceived with the advisory board was really the idea of doing a recently deceased human study. We tried to do some traditional cadaver studies. Some of you who are familiar with the orthopedic industry will see that there are a lot of devices that do cadaver studies and use the cadaver as a way to really get data for approval. And we tried to do those studies, and what we found is cadavers didn't have representative tissue compliance, either due to rigor mortis or issues of refrigeration or freezing of the cadavers. And we did a lot of work trying to make them more representative and then realized we really needed something that was more tissue compliant.

And so what we did is put together a study. It's a three-site study and -- two of the investigators are here today -- were under IRB approval and with consent. So we approached families of patients who are imminent, where comfort measures, for example, have been administered. We approach the families, and consented patients are then enrolled into the study, and once the subject passes and is deceased, we inject foam into the

abdominal cavity. And we used the study, then, to monitor things like pressure and organ contact and compare that back into the swine.

So this has been really the effort we've made to try to be in the most representative model prior to human use. And, again, this is something Dr. King will describe in more detail in tomorrow's session.

So that's kind of what we've done today. And part of the mission of today's session is to talk about some of the risks and the challenges. And one of the big challenges I think we face going forward is sort of the questionable regulatory strategy, and I think people up here have brought that up. And I think the regulatory strategy is so key because it drives the clinical plan and then it also drives the funding strategy. And as a project that is funded by the DoD, there's a whole cycle involved in terms of setting that plan, getting the funding, having that plan change and getting funding.

So what I'm going to show you over the next couple slides is our proposal for what the regulatory strategy is. This is again coming from the company. This isn't something that -- you know, obviously we're going through the FDA process now.

We believe, based on the data that we put together, the Arsenal foam is moderate risk, and that's given the intended use, as we've described. So these are patients who are very sick, Class III or IV hemorrhage that should die without immediate control of bleeding. And I think we have

heard this morning that there is a lack of alternative treatments for these patients.

And I think Dr. Ashar spoke earlier about, sort of, what is the burden of data and spoke to probable benefit outweighing probable risk. You know, based on the data that we have collected to date, we believe that the probable benefit outweighs the probable risk for this patient population. And that's based on the hundreds of swine experiments we've done and also then translating that into the recently deceased study. And I think an important part of that is the device design is simple to use, so taking away some of the complexity of the design piece. And also the training program needs to be very robust to support appropriate diagnosis of patients.

Now, that said, our intent is to push this out to the civilian setting, and one thing that's clear is, for clinical adoption, there is going to be a need for postmarket surveillance and potentially even a postmarket study. And so that's something that we are planning to do.

And we've looked at a number of regulatory pathways. The 510(k) pathway requires a substantially equivalent device. At this time we don't believe that there is one, so that's a pathway that we don't think is the appropriate pathway. Today we believe that the most appropriate pathway is the de novo pathway, where special controls would provide a reasonable assurance of safety and effectiveness for a moderate-risk device.

The other pathway that we've looked at and talked about is the

expedited access PMA. And for those of you not familiar, this is a recent draft guidance document that was issued in April of this year, really intended for devices and therapies for life-threatening conditions.

I think some of the things that we've thought about are: Does this pathway push us more into a need for a premarket clinical study? Does being a Class III device make it more likely that we're going to have longer review times? Having a guidance document that is draft and that is recent, as recent as April, there's limited experience. So, in some ways, you don't want to be the pioneer with this kind of thing. You don't know how that's really going to play out. Being a Class III device also has bigger implications for marketing changes down the road, and for a product like this, this is a low-volume product that could be extremely burdensome. So going back to the principles of sort of least burdensome approach, we believe that the de novo pathway is the appropriate pathway.

And that pathway would really rest on a number of proposed special controls. I think I've touched on some of those, but just to run through them. Diagnosis is a key part of this and making sure that we really have the appropriate patient, and that's having the indication statement reflect the intended use, really making sure it's those patients that are the sickest patients and having the training and certification to back that up. And I think, then, coupling that with usability testing, having users both on the military side and the civilian side demonstrate that they know how to use the

device, and then doing safety monitoring, postmarket surveillance after clearance of the device to ensure ongoing monitoring.

There's been a lot of discussion today about pre- versus postmarket. And just from our perspective for this device, I think there are a lot of internal concerns about (1) how we would fund a premarket study and (2) the overall time implications of getting this device out there.

You know, I think we've heard a lot about the need today. We've heard in some cases, premarket studies, just sort of getting the IDE process can take long periods of time, just getting through that IND/IDE process. I think a conservative estimate is that it could delay launch of this device by two years to have a premarket study, and that's through the flexibility of the protocols, that's through how the study is designed, what the eligibility criteria will be, et cetera.

So from our perspective, we believe a lot of the same things could be achieved in a postmarket study, an observational study, or using a registry, and we think that's also more consistent with the trauma population.

So, just in summary, we've done a lot of swine; as I talked about, 600 swine. Part of the reason we've done so many swine is because there have been so many questions in subpopulations that we've wanted to study, and we wanted to use a very robust and reproducible model to do that.

We've coupled that work with this study on recently deceased

subjects, which to our knowledge is the first time this kind of study has ever been done. And this work has been published in six publications, as I mentioned, and at eight presentations at national meetings. We are in the process of developing a training and certification program that will be robust to ensure that only appropriate users get this device, only appropriate patients get this device. And we're planning postmarket surveillance, and we're planning for a de novo 510(k) pathway.

Thank you.

(Applause.)

MS. KUMAR: Thank you.

Now I would like to introduce Ron Kaye, who is a human factors expert within the Office of Device Evaluation in the Center for Devices and Radiological Health.

MR. KAYE: Okay. Hello, everybody. Thank you for the opportunity to talk to you about human factors for this type of medical device. Of course, this is all new and emerging, and I'm not going to be able to tell you -- or wouldn't -- exactly how to make these things. We're just going to talk about some interesting concepts about human factors that are good to think about in the context of the use of these devices -- maybe. Okay.

Human factors is kind of a buzzword that's gained a lot of popularity. There is human factors engineering, human engineering,

usability, ergonomics, and all of these terms. It's essentially the same thing from at least our perspective. And the reason it is valuable is because when human factors engineering is done well, it will bring about better usability. So those are essentially synonymous terms.

There are some differences in how things are measured with respect to -- if it's just a usability test specifically, sometimes things are measured a little bit differently. There may be rating scales asking how easy it is to use and that sort of thing. Human factors looks more towards effectiveness and error rates and the occurrence of errors and that sort of thing, but it can be under the same heading. And when we review it, we're looking for work that shows that a device can be used safely and effectively with a minimum of errors.

When you think of the word "human factors" or the term "human factors," there's sort of a variety of elements to that. The human element, you might say, is our ability to perceive when we look at or listen to, touch, feel a device that is part of the process; the cognition of what goes on in our minds as we interpret it; derive meaning and understand what we need to do next; quite often, decision making. You know, the training that goes into a person's capability affects their cognition process in a certain way. Hopefully helpfully.

Then there are the actions, the actual physical interactions. Touching a button; is the button the right size? Or the control. Can you

control that, can you manipulate that control without inadvertently touching another one, perhaps, or with the right amount of sensitivity to get the outcome you're looking for when you're using the device?

So that's sometimes abbreviated as PCA: perception, cognitive, and action. It's a good way to start thinking about human factors and interaction with devices in a little bit more depth.

Then there might be the non-human human factors, but they're considered within human factors anyway, and that is the things outside the person: the use environment, such as noise and workload. And for this type of device, I think stress is quite important since you're dealing with somebody who is bleeding rapidly, and that likely will cause a lot of users of these devices to experience stress while they're interacting with it. Now, you might say, well, stress is not non-human, it's human. Well, okay. Well, stress comes from the outside, and that's kind of a non-human aspect; the experience of stress, that is human, absolutely. And then there's the medical device user interface itself, which is not part of the person or the user, but it is quite important. And we're going to talk about that some more.

It's perhaps helpful to conceptualize the user interface as any device. All devices that we use have them. Any device that falls into this category of hemostatic-type devices is going to have multiple user interfaces, likely. So the general perspective on how a user interface works in the context of use, if you go to the left side you might see that there might be a

display or there might be some labeling on the device. It might be molded into the device itself. But the user perceives that information, and then they go through a process of thinking about it or cognition, and hopefully, they understand what they need to do next.

And then they make some sort of control action, which is the physical part, and they manipulate something with the device. It might be opening a package, or it might be connecting one part of an accessory to another part of a device. It might be drawing up contents into a syringe or a pump reservoir, anything like that. But it's the physical manipulation, and that is input to the device, and assuming an electronic device has some smarts and will do some processing. But even passive devices that don't have that, often they change. So they either process that input or they change with the input, and they show you that through indications -- or it might be just the weight or there may be other cues, and then the user perceives that and continues. And this is a cycle that goes around and around.

But it's very important that this red band, which is the interface, is designed in such a way that it facilitates this process as best it can. And you can design devices, and it can be very difficult for users to use. They can make errors. But if you design it a different way or a better way, particularly if you have input from users, you can optimize this device. So we support the idea of optimizing the device user interface so all of these good things will happen.

So a good or optimized user interface design facilitates quick and effective use. And, clearly, that would be important here for these devices. It also prevents use errors or makes them less likely, okay, considering things like under-dose or a variety of other types of results that you wouldn't want. The interface should do what it can to prevent that from happening, to cue the user, even prevent the user from doing certain things. Or if you can't eliminate it, to make it as least likely as possible. And a good or optimized user interface design supports the ability of the user to leverage the clinical advantage offered by the technology of the device.

Another example of a device that's used in an emergency situation where someone is in dire threat of expiring is automated external defibrillators, and those are designed such that a home user, the ones designed for home use, can open it up, place the electrode pads, do all the prep and press the shock button if necessary and it has -- in that case they have a sequence of auditory instructions to tell the user exactly what to do, and that is part of the interface.

So design defects or inadequacies: As I said, there can be poor user interfaces. They essentially do the opposite of what a good one would do. They would allow use errors that could be prevented, and in perhaps the most sinister case, they actually lead users down the path of making errors that they otherwise would not make.

So considerations for the design of the user interface: This is

quite abbreviated, but at a very high level, it's important to think about who the users are. Is this device going to be appropriate for somebody with a high school education, perhaps less? Or are they going to be a trained surgeon? Are they going to be a home user? Are they going to be in a combat theater and a soldier with their training? But it's important to understand who the users are and what their capabilities and limitations might be when they interact with the device. And the idea is to optimize the design for the users you anticipate.

And then there is what needs to be done with the device. Any device that's used can be -- the interaction with that device can be broken down into tasks, and it's very helpful to do this because you get a lot clearer picture of what users are doing. And if you start looking into it and doing some user-centered design, you might see certain problems happening at a certain point, and you can say, well, this is when they're doing -- Task Number 17 seems to be a problem. Or you can look at all your tasks and say these are the most important ones. We're going to focus most of our attention on making sure that these are done, can be done well. So breaking down the interaction of the device in terms of tasks is helpful.

The use environment: Again, high stress in this case. I think probably most people in this room have experienced a time when you were under very high stress, perhaps driving somebody who is critically ill to the hospital and many other things. Even dialing 911. But certainly situations in

which a patient is in peril and you have to take a lot of steps very quickly and interact with devices and device interfaces while you're doing that, it can make it much more difficult for small problems -- it can make small problems become much more challenging for the user. So there are challenges to optimize the user interface design to the extent possible.

Helpful processes for optimizing the design of the user interface. We break them into preliminary analyses for ease of understanding, and that is to understand, up front, the user needs for safe and effective use of these devices or any device; the user expectations, how do the users think the device is going to work; a task analysis, as I mentioned previously. You can also do failure modes effect analysis or a fault tree analysis type of risk analytic approaches, trying to figure out, okay, if they do this here, what's going to happen next? Or if you go all the way to the other end, if you get this result, how might that have happened?

So those are good techniques for understanding user interactions because users -- if there's any take-away from this, I think the most important would be that you don't really know for sure what users are going to do with a device until you see it or until it's evaluated somehow, until you actually have the opportunity to observe users interacting with a device, because users can do some very surprising things with technology, and a lot of that can be helped by changing the design of the user interface.

And I should back up for a minute and say that the user

interface not only includes the interface of the device from our perspective here, anyway, but it also includes the training, the packaging, all of the user information, anything that moderates or changes how users will be able to interact with a device.

There are also user-centered techniques. This is where you do bring users in and you experiment with how they can use the device. And some of these techniques include focus groups, which you're probably familiar with; interviews; contextual inquiry; actually watching people use technology in a real setting; and simulated use evaluations, which are probably the most powerful and can be the most formal, too.

So, in terms of human factors guidance, we do have an old guidance from the year 2000 which is still in effect, and that's what it looks like on the cover. It might be interesting for you. We do have a newer version that is still in draft, and that's what that cover looks like. When will it come out? When will it be final? I'm thinking it will be pretty soon, I hope. And I do need to mention that the draft guidance is not for implementation. It reflects the current Agency thinking only. I want to make that clear.

There are national and international human factors standards. ANSI/AAMI HE75:2009 has a lot of good information, and it's a good resource. There are IEC 62366 medical devices, application, usability and engineering to medical devices, which is an older standard now. It is recognized, at least most of it currently, and it is being updated. And I think the updated version

is going to be a lot better than the existing version, so look for that sometime this coming spring.

Thank you very much. That's my quick presentation on human factors.

(Applause.)

MS. KUMAR: Okay, now we are going to have our final panel session of the day. Our moderator will be Andrew Barofsky, who is the CEO of RevMedX. And at this time I'd like to invite the additional panelists that will be sitting on the panel as well.

MR. BAROFSKY: Hello. Welcome to the industry panel discussion. I wanted to start off by thanking the Agency for putting on a great day, a great workshop. It's been very informative to me. I think we've covered some critical issues. And I've got three small kids at home, and 4:30 is definitely the witching hour. That's where they get tired and cranky. So we're upon that, and I think we'll try to move through this and get everybody out to happy hour as quickly as possible.

So I think we have a couple of additional panel participants that have not been up before. If you don't mind just making a really quick introduction, I think it's Dr. Sudarshan and Dr. Ramsey.

Okay, thank you.

DR. RAMSEY: I'm Maynard Ramsey, better known as Mike Ramsey, and I'm the CEO and Chief Science Officer of CardioCommand,

a small company in Tampa, Florida, that has developed a hemorrhage control product.

MR. MARTINELLI: And actually, I'm Larry Martinelli sitting in for Dr. Sudarshan.

MR. BAROFSKY: Oh.

MR. MARTINELLI: That's quite all right -- Materials Modification. We have a product presentation tomorrow that we'll be talking a little bit more about.

MR. BAROFSKY: Thank you, thank you.

So I'd actually like to start the discussion by leveraging a comment that Colonel Rasmussen made earlier in the day regarding the commercial viability of these products, and just to bring that perspective, that this is an industry-focused session. And I think viewing things through the lens of a company that is trying to develop and commercialize and bring these products to market is very helpful and very much informs the overall discussion because, at the end of the day, there has to be market viability for the product on some level. Otherwise, you go through all of this development and all of this regulatory -- and all of this work to bring a product to market that is not sustainable and would no longer be available to the end users and the patients who so desperately need the technology.

So I'd like to start. Another theme that we touched upon today that I think I'd like to start with, in terms of posing a question to the industry

participants, is the distinction between the military and civilian markets. And I'm interested in learning more and hearing your perspective on how that impacts product design and whether or not you're actually making products that are military-centric or that these products are being introduced in the military market for purposes of funding, et cetera. But I think that's a place we can sort of have the discussion on distinguishing between those two markets.

MR. SPENCER: I'd like to make a comment about the military part, not just on the funding side. I think an important -- and this is the investor in me, not necessarily the entrepreneur. But the thing that I like about it is not just funding, but the research arm because the military doesn't screw around like, if your stuff doesn't work, they kick it to the curb. So they're very Darwinian -- and if your stuff doesn't work, you know, you've done some societal benefit for proving it doesn't work and freeing up thought and resources to go somewhere else. But as an investor, it sounds where you want early failure. You want to discover early on that this doesn't work so you can go work on something that does work. And that's a benefit I have personally observed in working with the military.

Now, they're cruel and heartless. If you want to please the world, go join the circus, right? If you want people to cheer you on, go into show business. But I like dealing with them because they're brutally heartless, and they're going to tell you if your stuff doesn't work or it does

work and here's why. And as an entrepreneur that loves your baby, that this is the most beautiful thing, that can be very difficult. But as an investor, I think it's crucial, and I also think it ties right in with the FDA's mission, frankly, to make sure that it's safe and effective. So that, I think, hasn't been addressed, that there's a strong benefit to working with the military.

DR. SHARMA: Yeah. So, speaking to our experience, if you look at the product that we've developed, I can tell you, based on having a VC arm and VC products in the company, we would not be developing that product without military funding; it just wouldn't happen. And, you know, we still have the question even sometimes today with the investors, does it make sense for us, as a company, to be doing this?

And I think, because the military has been carrying the lion's share of it and because there is a civilian market that is starting to emerge and becoming clear, it's become something that everybody is on board with. But I think it's those two pieces together. It's having that funding and taking it the lion's share of the way and then having the civilian market available to us. And I think without either of those pieces, it would be very difficult for this product to be commercially viable.

I think, touching on the question of the military piece versus the civilian side, when we look at the market, you know, we expect that the majority of the sales are going to be on the civilian side. So we've developed a product to be able to be used by the military in the more rigorous

environment. And that may be overkill for some of the civilian requirements, but we see, again, that these things have to go sort of hand in hand because of who is funding it versus where the majority of the market is.

That said, I think some of the speakers spoke to this earlier. You know, we don't really understand why -- if there is sort of reasonable assurance of safety and effectiveness such that it could be out there for the military side, why you would then, say, deny civilian patients who -- you know, I think Dr. Holcomb spoke to the need on the civilian side -- why you would say those patients can't have access to the device.

DR. FALUS: I would go with that there is trauma needs in the civilian and military settings. But a strategy was conditioned by FDA, which set a regulatory path in the operating room for scheduled surgery. We accept that, and we do believe that hemostat noncompressible for severe trauma should be tested for safety and efficacy in controlled environments such as the operating room and emergency room.

So our path was established by testing our products as an adjunct to hemostasis, and then after its approval as an adjunct to hemostasis, it will be for an additional trial as a primary treatment, meaning that we develop a technology that has an established regulatory path, that has commercial viability, and that is used both in the civilian and military setting.

MR. BAROFSKY: Lance, do you want to go?

MR. HOPMAN: Sure. Yeah, I just want to talk about market viability. So we didn't have any military funding on this, so we're looking at it primarily from a return of investment standpoint with our own development, and we thought that -- you know, like I said in my presentation, the military was really the market for this, and we still think that's primarily the case. But these devices, junctional tourniquets that I'm talking about anyway, are pretty risky, and the return might be pretty marginal because you have four devices out there. And with the injectable foams there are multiple people working on that, too. But, eventually, the DoD is going to want to standardize on something. So one company is going to do fairly well with these products, but the rest are not. So that's a pretty high risk when you don't have funding behind you.

MR. BAROFSKY: Dr. Alcorta.

DR. ALCORTA: Yeah. First off, I am the AMS representative. I'm not actually a vendor, if I may make that as a clarity. I think this kind of discussion really lends itself well to looking at existing technologies and marrying them when appropriate. For example, when we talk about the intra-abdominal tamponade devices, we really should also be talking about FASTs and the appropriate indication in the civilian sector. The military clearly has a model; penetrating trauma explosions are a big deal. But what's the majority of what non-urban centers -- but the majority of our trauma centers are seeing blood trauma, and there's very clearly noncompressible

lesions occurring in the abdomen, where if you marry this with a device, it tends to increase its sensitivity and specificity. That is extremely important and it reduces complication rates.

So I think when we start talking about funding strategies, you also need to look at existing resources and technology to improve safety in the development and implementation of these devices, not just as a standalone. So I clearly see this kind of setting -- at least the presentations we've heard today -- having clearly a model in the civilian sector as well as military modeling.

MR. BAROFSKY: Thank you.

Teeing off of the comment regarding safety and switching gears a little bit, I wanted to loop in some of the prior discussion about human factors and how it relates to device design. A lot of these devices are going to have the potential to be used by clinicians with varying degrees of skill set, different backgrounds, et cetera, and I would appreciate it if the industry participants could discuss a little bit about how human factors elements actually impact the device design.

DR. KRAUSE: Let me comment first. I'm not from industry, I'm from the FDA, but this is a good place to throw in a plug for the early feasibility program because those types of studies can be done while you're tweaking the device, and human factor-type studies is a good place to be tweaking the device.

So early contact with FDA. Ron, who was up here, has an excellent team of individuals that work with him, who can really give you good advice on how to design your studies, how to interpret those studies, and to work on tweaking the device in early feasibility-type studies and things like that so, you know, also maybe get some early clinical experience. That's all things that the FDA is working on. So, you know -- and I think can be helpful. So I'd also like to hear what industry has to say.

MR. HOPMAN: I'll start off. So just from a very early standpoint in development, we've had a lot of help from special operations medics. We've had academic and clinician input as well. But these guys are very intelligent, so they can handle a device or a prototype or an iteration and say what is missing from what they need and then they can also have -- or they have the ability to step outside themselves and put themselves into the position of a soldier, a non-medic or a combat medic, and say, you know, my guys or some of these guys we see out there will do this with the device, and you can iterate based on that. So even before it gets to even a functional prototype, you already have that input.

DR. RAMSEY: Circling back on the civilian versus military needs and applicability, the device that I'll describe tomorrow was motivated by a hunting accident, clearly not a military event. But we've tested it with military people, medics in the field. And I totally agree, they know what they want, and they'll tell you what's right and wrong with it. And if you adjust it

and modify it to the way they're suggesting, it's usually a better thing. And we've done much of that.

MR. BAROFSKY: Thank you.

MR. MARTINELLI: Building on that and on the human factors side and usability and who's going to be using it, when we looked at this -- and the reason that we kind of leaned in the military side a bit more is because they are a very focused customer and they are a very focused user and they have specialized training. Now, maybe the average soldier gets himself some buddy help and self-training in that, but the medics certainly are top notch, and they know the kind of injuries that they are going after. So, for us, we looked at that as an important part of the usability of our product.

And then the whole concept of its simplicity. So from the very initial part, from a human factors perspective, we said it must be a hand-operated device. No mechanics, nothing of that sort. Now, there are other ways to do that. We have other iterations; we are in the process of that. But the truth of the matter is, it was a very focused client who had a very specific need, and we felt that we could best address that need and then move it out into the more general marketplace, which requires a lot more advertising and convincing and what have you on that.

MR. BAROFSKY: Thank you.

Colonel Rasmussen.

DR. RASMUSSEN: Well, I'd like to -- go ahead, please.

DR. SHARMA: So just building on that a little bit. You know, I think we've done the same thing, where we've tried to make the device very simple to use and have gotten a lot of medic input to really drive the design to answer a lot of these usability questions so that you can think about a military user who's an advanced medic versus a civilian user who may be a physician, and the device is appropriate for that entire skill set.

But that said, we do recognize that at some point when this gets out more broadly to the civilian side, there's likely going to need to be a redesign because some of the things that we've had to do to make it highly mechanized are not going to be things that people are going to want to do in the civilian side going forward, and are not going to be things that you need to do because you have power and because you have CO_2 gas and things like that. So, you know, we do recognize that that will probably diverge at some point, but for now we're trying to keep them together based on some of the conversations we had earlier.

MR. BAROFSKY: Thank you.

DR. RASMUSSEN: So I'd like to congratulate everybody at the panel. Tony Pusateri talked about some of the easier stuff. You know, this is the hard stuff here. This is noncompressible torso hemorrhage, junctional hemorrhage -- and the people at the table, the innovation, the effort, and the investment that has been made -- this is the hard stuff, okay? So I think we

need to acknowledge that. It's very responsive to the burden of injury and the epidemiology we talked about. So I think everybody is to be congratulated, and it's very exciting. And I want to say that and to thank and congratulate everyone.

Having said that, I think we have to act, right? All of these technologies are very, very similar in some degree, and we're dancing around the fact that we need human use and we need human use soon. I mean, don't change it until we use it in 10 or 15 trauma patients who are bleeding to death. And it seems like whether it's any one of these devices, it just seems like we're gilding the lily to get so close and then, oh my God, we better gild a little more. You know, let's get it in and let's try it. Let's try it and let's see how it -- it needs to be done in a responsible way.

But I would encourage -- this is a working group, and so working groups come up with ways forward. And I think we've got everybody here, it's the end of the day and nobody is leaving, everybody's coming back tomorrow. So I would challenge this working group to work and to find a way forward with about four or five technologies that just need to be used in about 30 or 40 patients.

And the burden of trauma is out there, and we in the DoD are investing in it, we're investing in a burden of trauma that's going to happen over the next 1 to 18 months. Those patients are going to be injured, and we're investing in their study. Whether it's in prehospital plasma, we've

invested the money.

Now, what we need is to find small segments of those patients and to try these devices. And it's not downrange; it's here in the U.S. And that will do a couple of things. It will help you hone your devices, which have been honed, largely. All of these have been honed to a large degree. It will socialize them in the public and foster a business model, and it will tell us if they work, it will tell us if they work in humans. And to Mr. Spencer's point, yes, some may not work, but let's figure it out is what I would say.

But I would end by congratulations. You're really tackling the hard stuff, but don't let this working group off easy. We've got to find a way forward.

MR. BAROFSKY: Thank you for those comments.

MS. KUMAR: I think in an effort to echo several of the comments that have been made here, and starting with the early feasibility study that Dr. Krause had mentioned, you know, we've heard a lot today about the interest in postmarket studies, so get the device in the hands of trauma surgeons and try it in a handful of patients to see what that looks like.

But we've also heard that the need for these products is at the point of injury, and we've heard that the trauma surgeons are not at the point of injury; the paramedics and the EMS workers are. So we have to find that bridge, and that's specifically what the early feasibility studies and some of these strategies that we need to come up with should address. So, you

know, get the device out there, and as you had commented, Upma, to then iterate on it and to have conversations and do some of the human factors research with the paramedics, with the field medics. You know, we know that you're all talking with special ops and they're walking ERs. There is a connection that can be made and the iteration, as the devices go on, that we can develop.

DR. RASMUSSEN: You're correct. And I think that's an excellent point, and I appreciate your insight into it. But there are a subset of patients who the point of injury is the resuscitation room. I mean, they come in quickly, and they're right there. We know that there are about three different kinds of patients that come into resuscitation rooms: those patients who come in dead and have been dead; patients who are actively trying to die; and patients who have injury patterns who are prone to try to die. There are a subset of patients who are just as if they are at the point of injury.

And as John said, a lot of these things I would start in the resuscitation room of busy trauma centers, under the guise of licensed emergency medicine physicians and surgeons and such and then move out. Set them up in a scenario that's prone to win, that's safe, that's supervised. Definitely don't try any of these things outside of the hospital initially. But Tom Scalea will see five wounds tonight, Shock Trauma, that are amenable to the XStat. He'll see them, and they'll be in the trauma room. They'll be bleeding in the trauma room, and Tom will go over and have to put a

tourniquet on it. So don't start out in the field, where human performance is going to be challenging. Set it up in a scenario where it's prone to win and succeed and be safe and overseen, and then get your experience there and then move it out, is a comment to that.

Go ahead, John.

DR. HOLCOMB: Yeah, I would concur with what Todd said. We are pretty aggressive in Houston with our helicopter system. You know, we have LVADs and ECMO and blood products and tourniquets and Combat Gauze and tourniquets, but they didn't start there, you know; they started in the hospital. And what we have told -- I trained medics for the last 20 years, and surgery residents, and still medics -- it's okay, you can do stuff, and if you screw it, it's okay. I can fix most of the stuff, but you've got to give them to me alive. But not a single one of those interventions -- and you go back in time and talk about the chest tubes, intubation, central lines -- none of those start at prehospital; they start in the hospital. We kind of validate them, if you will, and the validation may not be completely rigorous, but you want to make sure it works before you hand it to your prehospital partner. I think it's a really important point.

Clearly, the biggest bang for the buck is prehospital, no question. But as we've talked through, you know, many of these devices -- and I interact with many of the companies and others -- would start in our hands first. Then you make a collaborative decision, and if everybody is in

agreement -- docs, nurses, medics, different kinds of doctors -- then you go prehospital with it.

MS. KUMAR: Right. And just to clarify, I absolutely agree with that, and I think it goes back to Dr. Ashar's comment, where do we start? And I think what you're proposing in the prior conversations, that is the absolutely appropriate place to start. I think iterating on that as we go forward, you know, with the appropriate considerations from the end users as it moves forward, would lend to the most robust --

(Off microphone comment.)

MS. KUMAR: Um-hum.

DR. HOLCOMB: Risk and benefit. But it's not where we finish.

MS. KUMAR: Right, absolutely.

DR. HOLCOMB: That's absolutely not where we finish. I think we have really good agreement on that, but it's also the place to start with just about everything we've heard here.

DR. KING: Yeah, the point here is to have control, right? You can't just put this stuff out there willy-nilly. I'm sorry, Todd, you can close your ears, you have to hear this again, but the analogy I keep drawing is with CPR. In 1975, CPR was for doctors in hospitals, and that was it. It was absurd to think you could teach somebody else. A layperson on the street, seriously, is going to do cardiopulmonary what? And now your kindergarten teacher knows CPR. It's everywhere.

I'm not proposing a variety of hemostatic interventions that are going to be in everybody's pocket, but the point is it starts in a place with a high level of sophistication with very skilled end users, and you determine from there what's reasonably exportable. Some things will be a big win, like CPR. And maybe any one of these technologies will be a big win and will be exportable, but it has to start in a realm of high sophistication and control.

DR. ALCORTA: CPAP is a classic example of exactly what you said. It has reduced intubations dramatically and saved lives, but it took technology from the in-hospital setting to come to EMS.

DR. RASMUSSEN: I would go so far to say that some of these I would take into the operating room first. So the foams, I would randomize patients who have committed to a laparotomy. They have a positive FAST, and the surgeon has said this patient is getting a laparotomy and they go to the OR, and they either randomize to foam or no foam. So start them even in a more controlled scenario where you're going to operate on a patient anyway. Or the same with the balloon or the CRoC clamp. I mean, some of these things can be started in such a controlled fashion that we get some use, and that certainly is better than another pig or another 600 pigs or, you know, more than that.

MS. KUMAR: Premarket or postmarket?

DR. RASMUSSEN: As soon as possible.

MR. BAROFSKY: As soon as possible.

DR. RASMUSSEN: That's what the working group should --

MR. BAROFSKY: Yeah.

DR. RASMUSSEN: Well, postmarket. Yeah. But I mean, that's what we have to decide, a way forward. Yeah, postmarket.

MR. BAROFSKY: On that comment, I'd like to pose a question to one of the FDA representatives on their thoughts about how the FDA regulatory scheme could support the "let's just get them out there" approach.

DR. KRAUSE: Well, that's a difficult question. You know, I think you have to look at it in a lot of ways and I think, you know, as Dr. Ashar pointed out earlier, it's benefit/risk. I think products that are to be used in a population where the benefits far outweigh the risks lend themselves to less premarket clinical-type testing because the benefits are fairly obvious. And even though there is risk, risk of failure is -- I mean, it's going to happen anyway, right? So I think in some of those situations, reasonably good premarket data might be able to obviate a premarket clinical study and lend itself to a good postmarket study to make sure everything is working as advertised. You know, I think that's part of where this working group needs to go, as Todd was pointing out, and I think that's really what we're hoping to hear a lot more about.

DR. ASHAR: Yes, I just wanted to echo Dr. Krause's comments and emphasize the early feasibility framework. I know that we mention that term, and I think, conceptually, we understand what that means. But,

actually, FDA has a guidance document about early feasibility studies and the role that those can play early on in the device development process, getting subjects, patients exposed to the product in a way that is going to inform development.

And so, actually, our champion for our division is Dr. Betsy Ballard. So, hopefully, if she's here she can chime in, but I'm channeling her because she seems to be finding several opportunities, not only in the hemostatic product arena but in several first-in-human type of scenarios, where this is an approach that some companies have taken and are embracing. So this may be an opportunity to do the types of operative, controlled assessments that would give you the information that you would desire.

DR. KRAUSE: I'm going to put in a plug for my earlier talk. I did include a link to the early feasibility guidance, and also that has Betsy and Long Chen, who is our other champion in our division and has their e-mails for you to contact. Again, you know, I think five people or so sent me e-mails, and I've already responded to them and sent my talk. So, if you'd like, you can send me an e-mail, and I'm happy to send it and it does have a link to the early feasibility study page where you can get that document and look at it.

MS. KUMAR: We'll also be posting all the slides to which the speakers agree on our website for the workshop.

DR. BOCHICCHIO: I just wanted to throw out the same

question I brought out earlier. I'm sitting between, and I'm just using my academic hat. As a trauma academic surgeon, I have two foams; one goes through a Phase I, Phase II, Phase III regulatory pathway that the FDA has mandated, and I have another one saying they want an IDE postmarket. The same concept, the only difference is the chemical composition is different, just like if you're using the fibrin patch, like an EVARREST versus chitosan patch. Totally different.

So how do we get some advice from the FDA? Because you're talking about industry spending a lot of time and a lot of money trying to answer a question that we want to answer, but there is no clear direction here, and I know that's what the purpose that this meeting is for, to talk about -- because we talked about the need, but we still haven't talked any at all about these regulatory pathways about postmarket registries.

But if we have a product that's millions of dollars, gone through funding from NIH, DARPA, military, that is going through a Phase I, has to go through a Phase IIb/III, just like an Ethicon study that's all funded by mostly money from government agencies -- we talk a DARPA grant -- and I just think that we need to get our hands around, going forward, that there should be a little bit more transparency and clarity for these people who are working day and night trying to get a product off the ground.

And I see Bill laughing over there because he's an expert in this and understands this, but it's something that we really need to shed light on.

And I won't say it again, I promise.

DR. KRAUSE: I can comment on that really quick. Hang on a second. And I don't want to belabor the regulatory issue, but sometimes the FDA's hands are tied by the regulations and the law. And devices, we have Class I, Class II, Class III, and we have the de novo process.

Your product, as a fibrin sealant, it's regulated by CBER. CBER has -- you know, I don't want to speak for CBER, but you need to talk with the people in CBER who are regulating your product to see whether they can use another regulatory path. Can they use a de novo for this? I don't know, and I don't want to speak for CBER, but if they can, then maybe your path could be different. Right now, all of the fibrin sealants that I know of have all gone through BLA, and because they go through BLA, there is a required regulatory path. I don't know necessarily that a required regulatory path is the right terminology, but it's something you need to discuss with CBER. And the law is different for devices and biologics and drugs.

So while FDA -- and we talk with CBER all the time, and we try to use similar endpoints for products that are similar, but it's very difficult to try to merge different laws. So a visit to Congress, your congressmen, and pushing Congress to do things is sometimes the best way, but it's hard for us to apply or to give you advice on how to use a device pathway for a biologic.

DR. FALUS: Well, we have a device path, and you think it's reasonable and we are following it. We just believe that the Department of

Defense could make some effort to reduce the burden, just reduce it a little bit, because on considerations of national security many of them think they should break up or could reduce. Instead of having 200 patients, 800 patients. Then we have --

MR. BAROFSKY: I just want to check in on time. We're past due, and we're actually into the recap portion of the day, and I'm happy to sort of actually morph this into that, if it's okay, but --

DR. KHEIRABADI: Can I make a quick comment?

MR. BAROFSKY: Oh, sure.

DR. KHEIRABADI: Because it's really important.

MR. BAROFSKY: Okay, absolutely.

DR. KHEIRABADI: I have a bit of concern about the idea of taking this product directly to the OR and let's test them. And I'll say why. I mean, Dr. Holcomb is telling us the best chance of survival of this patient is to get them to the OR and do the laparotomy and fix it. Now, we bring them to the OR and say hold on. Let's first push this foam into them to see if it works or not. So then you come into -- I'm just saying that. So this is the conundrum. You have a standard of treatment. If you believe it works the best, you're going to put that on hold off and say, okay, I want to try to test this product to see if it works or not. I think that's not going to be ethical. It's going to be a problem that we have to somehow answer to it.

MR. BAROFSKY: Thank you, a very good comment.

MR. SPENCER: I just wanted to be slightly contrarian around the discussion of speed. And I think nomenclature is important. So here's my investor hat again. I think more important than speed is certainty. So I've heard a couple of terms: clarity, transparency. Those are, to me, rather loaded terms that might reflect some frustration, but I'm not sure they're particularly fair, given the environment that the FDA has to work within.

But I do think that the efforts to bring certainty to the process are of value, and that's why I applaud things like early feasibility or other efforts, which I see are attempts to not speed the process as much as they are to reduce the determination of certainty. And I'm not talking about certainty of outcome; I'm talking about certainty of effort and certainty of cost. And as an investor, the biggest challenge with dealing with devices in the wild, wild west that is the trauma community is bounding your costs and bounding when you know you've failed or whether you've succeeded.

And so I applaud all arguments for speed, but I think we might behoove ourselves if we include in the conversation that some certainty of effort and certainty of cost are of great benefit and really what we're trying to get here. Not necessarily rush, rush, rush, rush, rush.

DR. SHARMA: So I want to come back to some of the comments on the -- sorry.

MS. KUMAR: No.

DR. SHARMA: The early feasibility. It's something we, as a

company, have looked at and I think honestly have some concerns about. And I think it's when you read the guidance document that early feasibility doesn't really accomplish, I think, what we're trying to do here. It's really written to be a study prior to a pivotal -- more like a Phase III study. And I think if we start going down this path, our concern is that we're going to end up doing a large premarket randomized study to try to show safety and efficacy before the device ends up getting out there, just based on the way the guidance document is written. And so I think that's one concern that we've had with that pathway.

MS. KUMAR: I think that we're here because -- you know, we called this meeting because we have seen the need to think outside of the box, additionally, and I think the early feasibility guidance, as it's written, is a place to start. But it's not the end-all, be-all of what the early feasibility program needs to be.

And we also have used other mechanisms such as confirmatory trials, and there can be a hybrid approach to those, especially for the products that have a very dramatic benefit/risk profile such as that.

So I hear the concern, and I think that has been encountered with other types of early feasibility programs, and as it's written in black and white, that is one use that it could be. But I think that we have the opportunity to think outside of the box on this and can come up with alternative approaches.

DR. RASMUSSEN: I'll end where I started and just again congratulate you on your work and for convening the working group.

And I think, again to emphasize, to follow on that comment, you really are looking at disruptive technologies. I mean, if you -- to the concept of tackling noncompressible torso hemorrhage is something for trauma is something that -- that is a disruptive technology, whatever it is, which, you know -- and junctionals in the same way, especially in the trauma setting, emergent setting, the dying patient, the patient is trying to die.

So, you know, your comments are very much -- they're very apt. I mean, it's true to think about outside of the box, and it's a challenge, and to your credit you've convened this and held this challenging discussion. You know, not to overstate it, but in a way, we are sitting here similar to the debate of taking CPR out of the hospital, you know? I mean, you really are. Are we really going to let AEDs out of the hospital? I mean, they're going to shock people. And wouldn't it have been interesting to hear what those discussions were like, however long ago they occurred? You know, David, to your comment. So I challenge all of us to think about this tonight, but then to try to think about clear ways forward.

But, again, I end by just telling you, thank you for convening this and for everyone at the table for really tackling these disruptive technologies and this tremendous problem of bleeding. So I'll end with that, or at least I will thank you.

MR. BAROFSKY: Thank you. I actually think that's a great way to end the panel discussion. And I agree, disruptive technology means that you're implementing some pretty drastic change, and that can be hard to do.

So I applaud the panelists as well. I thank you for contributing. And I think we're moving into the recap, if that's right, or -- Allison? Binita?

Thank you.

(Applause.)

MS. KUMAR: Okay. Well, thank you all for the extended time that we spent having that really good discussion. I think it was needed, and I think it's going to set the stage for tomorrow, when we talk about ways of assessing safety and effectiveness to get to those out-of-box solutions. So we're going to be hearing a lot about the different types of studies that have been done and are being planned to do to support the initial data in a premarket setting that would pave the way for additional ways to collect safety and effectiveness data in patients.

So I've heard a lot of feedback that FDA has a lot of workshops and whatever comes of them. So I don't plan to let anyone off the hook as far as this workshop goes. And we've heard the term "workshop, workshop, workshop," so we are actually going to work tomorrow. We're going to save the last 45 minutes of the morning session -- this is only a half-day session tomorrow -- to break out into small groups and very quickly and dynamically answer some of these questions. And I expect everyone in this room, as a

stakeholder, to have a voice in answering some of those questions and to see what group consensus is.

As you know, Dr. Ashar noted, we're not creating FDA policy here, but we need some feedback and we need some key stakeholder thoughts, and we've heard about the great minds that we've had in this room, and we've seen some of the hard work that's been done by the industry here. And, you know, we're going to hear from the researchers and others tomorrow. So we're all going to come together and really have some output from what we've learned and where we want to go. And FDA is going to use that to make decisions for some of these products.

So thank you for your participation today and thank you for your participation tomorrow, and we look forward to seeing you all back.

(Whereupon, at 5:10 p.m., the workshop was adjourned, to be reconvened the next day, Thursday, September 4, 2014.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PUBLIC WORKSHOP - HEMOSTATIC MEDICAL DEVICES FOR TRAUMA USE

September 3, 2014

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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